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SURGERY

A Monthly Journal Devoted to the Art and Science of Surgery

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SURGERY

VOL. 31 MAY, 1952 NO. 5

Original Communications

PATHOLOGIC CHANGES IN MEGAESOPHAGUS (ESOPHAGEAL DYSTONIA)

FREDERICK S. CROSS, M.D.,* MINNEAPOLIS, MINN.

INTRODUCTION

WILLIS is given credit for first describing a case of megaesophagus in 1672,[5] and cases began to appear with some regularity in the literature following Purton's[9] case in 1821. Yet, at the present time, there is still so little uniformity of opinion that there are at least 12 names given the disease, almost as many theories as to its etiology advanced, and present-day therapy is just beginning to coalesce into a rational approach which not only corrects the underlying disorder, but also prevents serious postoperative complications. The most concrete facts that have emerged from previous studies are concerned with the pathologic changes in megaesophagus. In 1924 Hurst[6] postulated that the lesion in megaesophagus was a destruction of Auerbach's plexus by a progressive organic disease. Rake,[10] in 1926, confirmed this idea by describing a case of megaesophagus with destruction of Auerbach's plexus seen at autopsy, and, in 1927,[11] added two more cases. This finding has been confirmed more recently by other investigators.[2, 4, 8] The changes are of sufficient interest to review them at this time with the presentation of nine cases.

PRESENT STUDY

Recently, megaesophagus has been treated in a new manner in this clinic.[12] The lower portion of the esophagus is resected along with the acid secreting portion of the stomach. The tortuous esophagus is then freed up as much as possible and straightened out by drawing it down and anastomosing it to the antral portion of the stomach. The first operation of this type was done March 3, 1949, and since that time six additional such operations have been done. To supplement the seven surgical specimens from these cases, material has been obtained from studies on two autopsies taken from the files of the Department of

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*Department of Surgery, University of Minnesota Hospitals.

Pathology. The ages of these patients ranged from 24 years to 76 years. The duration of symptoms ranged from one and one-half years to thirty years. The earliest age of onset was 10 years, and the latest age of onset was 74 years. The onset of symptoms was in the first three decades in five of the patients, and in the fourth, fifth, and eighth decades in the remaining four cases.

All specimens were opened along the greater curvature, fixed in 10 per cent formalin, and stained with hematoxylin and eosin, Nissl's stain, and Masson's trichromic stain. The blocks for sectioning were cut both transversely and vertically through the esophagogastric junction and from various levels of the esophagus as space would permit. All blocks were cut approximately 2 cm. in length. Blocks were also cut from the greater and lesser curvatures of the stomach for comparison. Multiple sections were taken from widely separated intervals in each block. Only those sections which were entirely satisfactory were studied for ganglion cel's. In all, 142 sections from the 9 cases were used for the study although many more sections than this were actually examined.

CONTROLS

Sections from nine esophagi not afflicted with megaesophagus were also studied to establish the normal appearance of this structure with special reference to Auerbach's plexus and the number of ganglia and ganglion cells present. These specimens were from both surgical and autopsy material, and the ages of the patients were from 45 to 80 years.

RESULTS

Grossly, the esophagi show varying degrees of dilatation with associated lengthening in the more advanced cases. The most dilated esophagus in this series is 14 cm. in circumference at the level of the hilus compared to 4.5 cm. at the cardia. In the same case there is thickening of the muscle layer in the dilated portion, the wall in this area being twice as thick as in the region of the cardia. In general, the dilated portion of the esophagus is separated from the stomach by an area of normal esophagus measuring 1 to 4.5 cm. in length corresponding roughly to the subdiaphragmatic portion of the esophagus.

The microscopic findings are the most significant aspect of this study. The seven surgical specimens and one of the autopsy specimens will be discussed together and the second autopsy specimen by itself because it differs significantly from the other cases, as will be brought out later.

There is an inflammatory reaction throughout the esophageal wall both acute and chronic in nature, much of the acute phase in the surgical specimens being due to operative trauma. The chronic inflammatory change with an infiltration of lymphocytes is most severe in the serosal and submucosal layers. The mucosa is intact in all of the sections. Fibrosis is present in the circular and longitudinal muscle layers especially in those areas where there is thickening of the esophageal wall. The most important changes are in the area of Auerbach's plexus. Ordinarily this is a thin, hardly discernible layer between the circular and longitudinal muscles consisting of thin fibrous tissue supporting frequent parasympathetic ganglia along with nerves and small blood vessels

(**Fig. 1**). In the diseased specimens this normal architecture is greatly altered. The layer of the plexus is usually wider than normal. There is an infiltration of mononuclear and polymorphonuclear cells and an increase in capillaries. The fibrous tissue reaction varies from a slight increase to a complete replace-

Fig. 1.

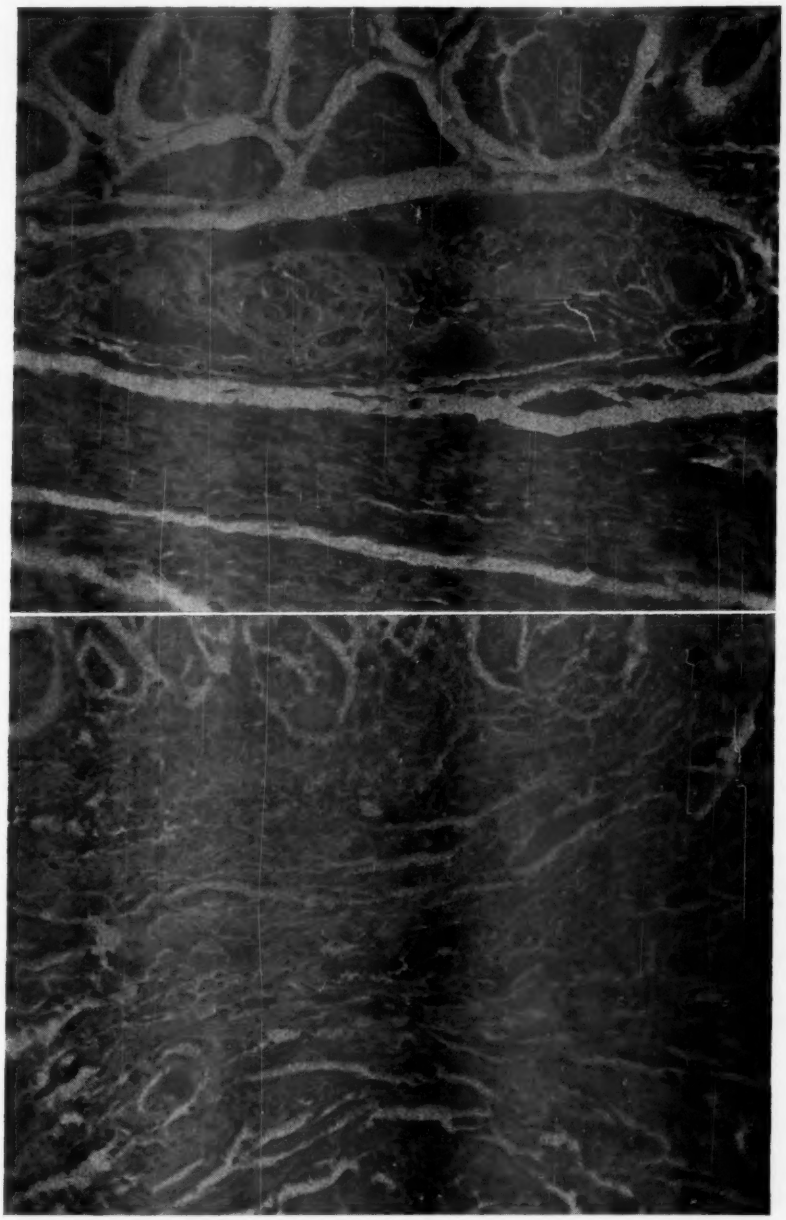

Fig. 2.

Fig. 1.—Normal parasympathetic ganglion from Auerbach's plexus with a large number of ganglion cells present. Note the clusters of supporting cells about the periphery of the nerve cells (×165).

Fig. 2.—Auerbach's plexus in megaesophagus showing a marked fibrosis and infiltration of inflammatory cells. There is wide separation of the muscle layers present. A poorly defined ganglion is seen (×90).

ment of the plexus in some areas by a dense fibrous tissue (Fig. 2). The parasympathetic ganglia are not readily discernible because of this fibrous tissue proliferation. In addition, many of the ganglia are almost completely replaced by small mononuclear cells resembling lymphocytes (Fig. 3). It is felt, however, that these cells represent a marked proliferation of capsular and extracapsular supporting cells rather than inflammatory cells. There is also an increase in the interstitial connective tissue present in the ganglia. The most striking change is the virtually complete absence of nerve cells from the myenteric ganglia. In the entire series of 117 sections studied from the first eight cases under discussion only three ganglion cells are seen. In some of the ganglia the shrunken capsule of a cell is still present but the cell within is gone, or it appears as a mere vacuolated shadow.

In direct contrast to this picture is the section shown in Fig. 1 in which a single ganglion is seen containing 11 nerve cells. It is not uncommon to find this many nerve cells in four or five ganglia in each section from a normal esophagus.

There is evidence that the loss of ganglion cells is limited to the esophagus. In sections taken from just below the esophagogastric junction and from various areas of the greater and lesser curvatures of the stomach ganglion cells are present in normal numbers.

The esophagus from one of the autopsies differs from the others in that it is the only one in which ganglion cells are found in significant numbers, but not as frequently as in a normal esophagus. The presence of nerve cells is undoubtedly explained by the fact that symptoms were present in this case for only one and one-half years; whereas, in the previous cases, symptoms were present from twelve to thirty years. The microscopic findings here represent the early changes in the disease. Ganglion cells are seen in various stages of degeneration. In the same ganglion, normal nerve cells staining blue with hematoxylin and eosin are seen along with shrunken, amorphous, pink-staining cells. About many of the ganglion cells there is a proliferation of capsular cells into several layers. In other areas these capsular cells have invaded the capsule replacing the ganglion cell. At first this process of destruction of the nerve cells is represented by capsular cells lying in concavities in the periphery of the nerve cells (Fig. 4). Later stages are seen in which a cluster of from five to twenty or more capsular cells are present with the vague outline of the destroyed nerve cell in the background. A single ganglion can show several stages of this destructive process, while others show the end result in which there is a complete loss of nerve cells with increased numbers of capsular and interstitial supporting cells almost replacing the ganglion as previously described in the cases of longer duration. Kuntz and Sulkin[7] describe similar findings in sympathetic ganglia as a process of neurocytolysis.

A total of twenty-five sections were taken from various levels of this esophagus in an attempt to note any difference in the number of ganglion cells found in each level. No significant difference was found. In the upper third of the organ, where striated muscle is present, no ganglion cells were found, a situation also true in the normal esophagus. In the surgical specimen in which

14 cm. of esophagus were available for study, no ganglion cells were found at any level, which seems to indicate that in the late stages of the disease ganglion cells are destroyed in the entire length of the organ.

Fig. 3.

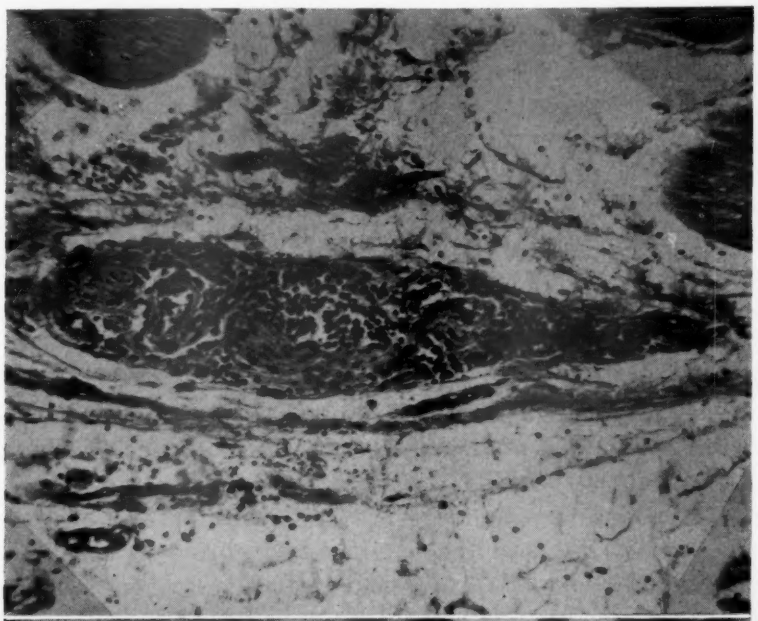

Fig. 4.

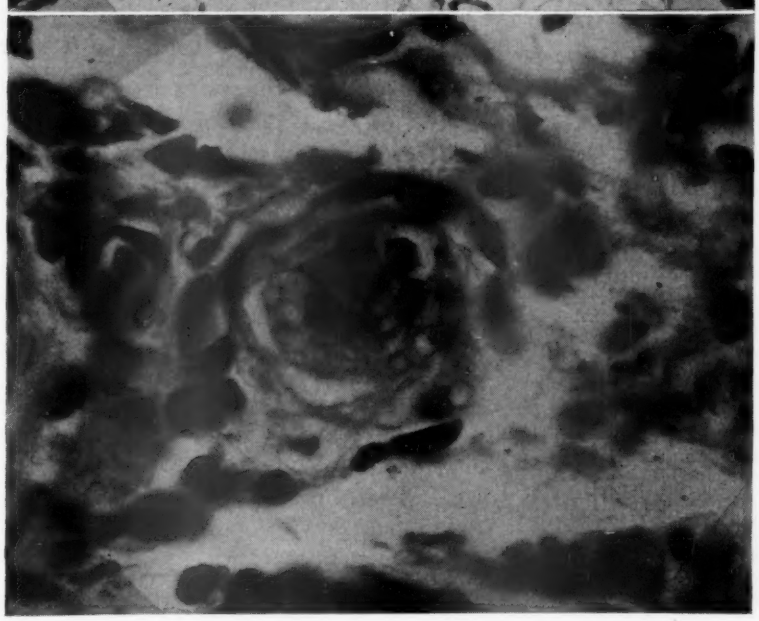

Fig. 3.—Degenerated ganglion showing complete loss of nerve cells and a marked increase in capsular and small interstitial cells (×165).

Fig. 4.—A parasympathetic ganglion cell undergoing neurocytolysis. The nerve cell is surrounded by a ring of normal capsular cells. It is vacuolated in appearance, and a capsular cell which has become spheroid in shape is seen in a peripheral concavity at the upper right (×650).

DISCUSSION

As yet there has not been a good explanation for the cause of these inflammatory changes and loss of ganglion cells in Auerbach's plexus. Primary vascular disease, congenital abiotrophy, infective ganglionitis, syphilis, and spread of inflammation from esophagitis have been mentioned as possibilities. Experimentally, these cells are extremely difficult to destroy. Cannon[3] states that the parasympathetic ganglion cells in this area are the most resistant nerve cells in the body to destruction. The sympathetic ganglion cells are only slightly less hardy. He deprived sections of the bowel of their blood supply for six to seven hours and the deprived areas recovered normal activity. Sections of gut were also compressed between glass plates for as long as three hours without loss of normal motility. If the compression anemia lasted for three and one-half hours or longer, however, it almost invariably resulted in loss of function and disappearance of the nerve cells. Alvarez[1] tried to destroy the ganglion cells in the myenteric plexus with various nerve poisons and with anoxia, but without success. He states that many of the nervous elements of the bowel are as resistant to anoxia as the adjacent muscle.

Slides from surgical specimens of twenty cases of chronic ulcerative colitis and regional enteritis were studied. The disease in these patients ranged from two and one-half to 30 years' duration, and the slides showed severe inflammatory changes of both an acute and chronic nature affecting all layers of the bowel wall. In spite of both the severity and chronicity of the disease, the ganglia and ganglion cells were present in normal numbers. This observation would suggest that chronic inflammation per se does not cause the loss of ganglion cells, at least in ulcerative colitis.

It is interesting that one of the cases in this series had active tuberculosis, another had tuberculous lymph nodes in the region of the lower esophagus, and a third had granulomatous lesions in the area of the myenteric plexus suggestive of tubercles. The other six patients had no history of tuberculosis, but they were not studied extensively with this in mind.

The question is often asked if this disease is congenital in nature. It is a difficult question to answer especially since megaesophagus is so often found in individuals in the older age groups. However, when the evidence is examined more closely it frequently becomes apparent that symptoms were first noted early in life. Weber[13] reports eleven cases from the literature occurring in the first seven years of life. On the other hand, the oldest patient in our series was 76 years old and had symptoms for only one and one-half years before his first admission to the hospital. Perhaps it may be pointed out eventually that there is both an acquired and congenital form of this disease.

Grossly, certain similarities exist between megaesophagus and congenital megacolon, but they differ microscopically. In megacolon, the ganglion cells are missing only in the narrow portion of the colon and are found in normal numbers in the dilated portion; whereas, in esophageal dystonia the ganglion cells are missing from all levels of the esophagus.

The loss of ganglion cells from the esophaus is accepted as the etiologic basis of this disease by some investigators.[7, 8] However, physiologic functional

changes in an organ cannot be explained by investigating pathologic changes alone. The loss of ganglion cells may be a secondary phenomenon rather than the primary cause of the disease. It remains to destroy experimentally the cells of Auerbach's plexus. If the syndrome of megaesophagus, as it is known clinically, could be reproduced, some indication of the nature of megaesophagus would be established.

SUMMARY

1. Seven surgical cases of megaesophagus and two cases seen at autopsy are presented in which the pathologic findings are described as an inflammatory reaction in the area of Auerbach's plexus with a loss of ganglion cells and replacement by capsular and interstitial supporting cells.

2. The destruction of ganglion cells is explained on the basis of a neurocytolysis of the nerve cells by proliferating capsular cells.

3. The necessity of further investigation is recognized to determine the true etiology of the disease.

Acknowledgments.—The author wishes to thank Dr. A. T. Rasmussen for invaluable aid in interpreting the changes seen in the microscopic sections and for lending encouragement to the project, and also Dr. Rudolph Koucky and Dr. Steven Barron for furnishing the autopsy material used in the study.

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OBSERVATIONS ON WATER INTOXICATION IN SURGICAL PATIENTS

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THE relationship of the state of hydration and the extracellular electrolyte concentrations to the occurrence of seizures is well recognized.[10, 34, 35, 37, 38] From the clinical standpoint, this relationship has received the greatest attention in connection with epilepsy, and one is led to believe that even Hippocrates was aware of the significance of hydration in the epileptic; for in the Hippocratic work *On the Sacred Disease,* seizures in epileptics are ascribed to the fact that the "brain becomes more humid than natural."[23] Although epilepsy has received the greatest degree of attention in this regard, it is apparent that the relationship of water and salt balance to seizures is qualitatively similar in all individuals, it being more frequently brought to our attention in those persons in whom the convulsive threshold happens to be low.

In 1922, Weir, Larson, and Rowntree described convulsions in an individual suffering from diabetes insipidus who was encouraged to continue his accustomed fluid intake after polyuria and polydipsia had been controlled with pituitary extract.[54] They found that this picture could be reproduced in the dog by the administration of pituitary extract and large amounts of water. These observations led to the extensive experimental studies of "water intoxication" which were subsequently carried out by Rowntree and his co-workers.[16, 17, 45, 46] In the early work on this subject it became apparent that the occurrence of seizures in experimental animals was related not only to the amount of water which was administered but to the availability of extracellular ions, and that the administration of sodium chloride could reverse or prevent the manifestations of excess water.[17, 45, 49, 51]

As will be seen, this point is of greatest importance in the consideration of the problem with reference to surgical patients. Helwig, in 1935, reported the accidental occurrence of fatal water intoxication in a patient following cholecystectomy.[21] He reported another, similar case in 1938.[22] Barahal in the same year reported the syndrome in a psychotic patient who voluntarily ingested extraordinary amounts of water.[4] Water intoxication is now recognized as a serious complication of parenteral therapy, a complication to which patients depleted of extracellular electrolytes are particularly susceptible.[32, 39]

The peculiar susceptibility of postoperative surgical patients to this complication is for both theoretical and practical reasons a matter of greatest interest. Ariel and co-workers, in 1950, reported instances of greatly enlarged

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thiocyanate space associated with central nervous system signs.[2] Two of these patients exhibited seizures. The present report deals with 17 patients who displayed convulsive seizures following surgical operations and in whom the clinical manifestations appeared to be on the basis of fluid and electrolyte disturbance alone. In some of these the situation resulted from ostensible errors in fluid administration. In others, entirely reasonable amounts of parenteral fluids were given. There was no difference in the clinical features of these two groups. Since convulsions occurred in two of the cases previously reported in connection with enlarged thiocyanate spaces, these two cases are included in the tables.

METHODS

For the determination of the carbon dioxide combining power, serum chloride, blood sugar, and urea nitrogen, the usual hospital laboratory methods were used.[41, 47] Sodium and potassium determinations were performed with either the Barclay or the Perkin-Elmer internal standard flame photometers. Because of the experimental evidence relating water intoxication to adrenal function (vide infra), eosinophil counts were done in many of the cases on the assumption that these counts, done within one or two days after operation, would be very low if adrenal function were adequate.[27, 44] In the early cases the eosin method of Dunger was used and later on the two-stain method of Randolph was adopted.[9, 42] In some instances, an attempt was made to evaluate adrenocortical reserve utilizing the eosinopenic response to epinephrine.[43] When this was done, a period of at least 14 days was allowed to elapse following the operation before the test was carried out.

The body weight of patients was determined before operation and daily after the procedure, utilizing the litter balance where patients were unable to stand on the ordinary scales.[52, 53]

RESULTS

Although it is likely that hydremia may be related to other surgical complications, only patients who developed convulsions are considered. There are 17 patients in the series.

Age Incidence.—Table I summarizes the clinical data on the 17 patients. The average age was 67.4 years. Older patients appear to be definitely more prone to this complication. Only one of the series (No. 12) was under 50 and this was the only patient known to have actual renal disease.

Type of Surgery.—As can be seen in Table I, the syndrome under discussion was observed in relation to a variety of surgical procedures. Considering the predominance of gastrointestinal surgery in this hospital, there is no particular association with this type of operation, though one might expect that the loss of electrolytes through gastrointestinal drainage might predispose to this complication. Four of the cases followed operations on the breast and chest wall. There seemed to be a predilection for the larger and more prolonged procedures.

Time of Onset of Convulsions.—Fig. 1 depicts the distribution of times of onset of seizures following operation. It shows that 16 of the 17 cases occurred

TABLE I. CLINICAL MANIFESTATIONS OF POSTOPERATIVE WATER INTOXICATION

CASE NO.	PATIENT DATE	SEX AGE	DIAGNOSIS AND OPERATION	ONSET OF CONVULSIONS (HR. AFTER OPERATION)	CLINICAL SIGNS	SYSTOLIC BLOOD PRESSURE 1. PRE-OP. 2. SEIZURE		TEMPERATURE (IN DEGREES F.)	OUTCOME
1	M. M. 793005 7/30/48	F 74	Ca. rectum; combined excision	31	Unconsciousness, seizures involv. sep. extremities, never generalized	140	152	98.6 (Axillary)	Confusion 10 days; complete recovery
2	G. B. 794999 9/29/48	M 68	Diverticulitis; partial colectomy	26	2 seizures, coma, areflexia	155	190	99	Coma 4 days, followed by confusion & hallucin., memory impairment; eventual recovery
3	E. T. 797761 11/26/48	F 68	Ca. breast; super-rad. mastectomy	40	Cyanosis & stupor, generalized seizure, hyporeflexia, Babinski's sign	150	168	101	Death in 12 hr.
4	J. S. 611953 6/17/49	F 77	Ca. rectum; ant. resection	23	2 seizures, coma, Babinski's sign (?)	170	240	98	Coma 4 days, complete recovery; re-op. 6 mo. later well tolerated
5*	J. J. 729986 7/28/49	F 72	Ca. stomach; gastrectomy, cholecystectomy, nephrectomy	31	Gen. seizure, coma, Babinski's sign	140	118	99.8	Mental recovery in 10 days
6*	A. L. 805574 8/3/49	M 82	Stomach ulcer; gastrectomy	26	Unconsciousness preceding 2 seizures	124	130	100	Coma 2 days followed by confusion, recovery in 1 wk.
7	M. H. 798609 8/29/49	F 68	Ventral hernia	31	Confusion followed by seizure & coma	160	130	99.2	Mental recover in 48 hr., complete recovery
8	F. C. 808761 9/15/49	M 72	Ca. stomach; subtot. gastrectomy, part. pancreatectomy, colectomy	41	1 gen. seizure, loss of consciousness	120	104	100.8	Return consciousness 1 hr., complete recovery; re-explor. 2 mo. well tolerated

9	B. B. 810020 10/14/49	F 76	Ca. rectum; combined excision	26	Gen. seizure, coma	130	160	98.8	Coma 24 hr. followed by confusion, recovery 1 wk.
10	M. H. 817978 5/19/50	F 53	Ca. tongue; gastrostomy	15	2 grand mal seizures, coma, hyperreflexia, no Babinski's sign	150	135	100	Recovery 24 hr., further surgery well tolerated
11	E. W. 825320 11/14/50	F 59	Recurrent ca. breast; excis. chest wall tumor	27	7 gen. seizures, coma, areflexia, no Babinski's sign	180	180	101	Profound coma 6 days, disorientation; ment. recov. 1 mo., memory defect persists
12	B. S. 785066 4/16/51	F 38	Osteomyelitis, amyloidosis with renal involvement; excis. of sinuses	48	2 gen. seizures with rapid return of consciousness	130	120	98.4	Recovery from episode; death 3 wk. later from uremia
13	H. H. 831326 5/8/51	F 76	Femoral fracture; internal fixation colostomy	11	Confusion & twitching movements 8 days preceding convulsion	110	124	100.8	Treatment caused diuresis and wt. loss, but patient died in 12 days
14	I. F. 832284 5/17/51	F 55	Ca. breast; super-rad. mastectomy	32	1 gen. seizure	180	150	101.4	Coma 2 days, grad. ment. recovery, memory defect persists
15	L. W. 831860 5/29/51	F 63	Ca. stomach; gastrectomy	21	1 gen. seizure, coma	140	160	99.5	Return of consciousness in 5 hr., complete recovery
16	R. G. 832606 7/6/51	F 71	Ca. breast; radical mastect.	22	1 seizure, coma reflexes normal, no Babinski's sign	140	160	102	Coma 2 days, confusion 3 wk., slight memory impairment, recovery otherwise
17	A. O. 833708 7/6/51	M 74	Ca. stomach; gastrectomy	19	1 gen. seizure, coma, Cheyne-Stokes respiration	148	130	101.3	Return of consciousness in 10 hr., death 5 days later from failure of anastomosis to heal

*Cases previously reported by Ariel and associates in paper dealing with enlargement of thiocyanate space.[2]

within 48 hours of the time of operation and that the majority occurred between the twelfth and thirty-sixth postoperative hours. This high incidence of seizures in a relatively confined interval of the postsurgical course is one of the most striking characteristics of the syndrome and one whose theoretical implications will be discussed later.

Temperature and Blood Pressure.—Experimental water intoxication in animals is characterized by hypertension and hypothermia.[18] In surgical patients where many other factors (inflammatory, hemodynamic, etc.) are at play, one might expect these phenomena to be obscured. Temperatures at the onset of seizures are recorded in Table I as are the systolic blood pressures before operation and at the time of convulsions. Temperatures ranged from 98.9° to 102° F. In no instance was the temperature extremely high. No constant change occurred in the blood pressure. It is of interest that in no instance was the picture accompanied by shock.

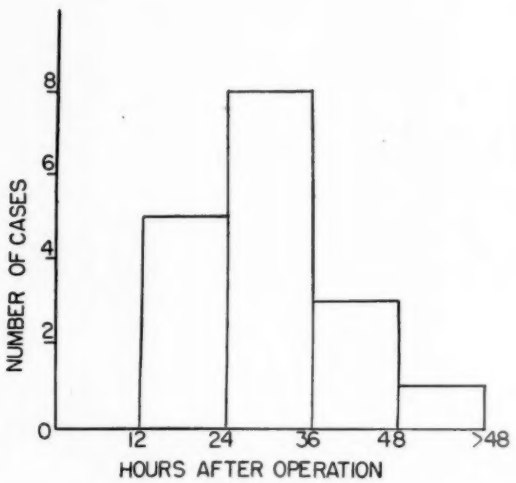

Fig. 1.—Distribution of the time of onset of seizures following operation in the 17 cases of water intoxication.

Physical Signs and Clinical Course.—The physical signs along with the course and outcome are briefly summarized for each patient in Table I. Seizures usually came on suddenly, in many instances the patients appearing entirely normal and alert prior to their onset. In 16 of the 17 cases, convulsions were of the *grand mal* type. They were followed by coma which lasted from a few hours to many days. Recovery in more severe cases progressed through phases of stupor and confusion, and finally protracted periods in which memory impairment was evident.

A variety of neurological signs were observed. These included inequality of pupils, hyperreflexia and hyporeflexia, and occasionally plantar signs. These findings changed rapidly from one examination to the next and varied greatly among the patients. Besides seizures and posteonvulsive coma, there was nothing common to all the patients. In no instance were localizing motor signs observed.

Three of the patients (Nos. 3, 13, and 17) succumbed. In one of these (No. 17) it is not clear that the electrolyte disturbance played a significant role in the fatal outcome, although one wonders whether the failure of healing of the anastomosis which was responsible for death in this case could have resulted from impairment of cellular activity by overhydration. Patient No. 3, the only one in whom seizures occurred late in the postoperative period (8 days postoperative), was a poor-risk, elderly patient with cardiac disease to whom daily administration of fluid without sodium chloride had been made for many days. When the extremely low electrolyte values were discovered, and treatment with hypertonic saline instituted, she responded with diuresis and elevation of the electrolyte concentrations. By that time, however, she was so extremely ill that survival was apparently impossible. It appears likely that the disturbance of hydration was an important factor in her death. Patient No. 3 died two days after surgery following generalized seizures. The significance of her weight gain, depressed electrolytes, and strongly positive fluid balance was not appreciated at the time. Post-mortem examination offered no explanation of her death, and it seems probable that she died of hydremia alone.

Blood Chemical Findings.—The severe depression of sodium and chloride concentrations in the serum of the 17 cases is seen in Table II which summarizes the blood-chemical data on these patients. Many of the sodium values were below 120 meq. per liter and three were below 110 meq. per liter. The chlorides were correspondingly depressed, two values being below 70 meq. per liter and the majority below 80. As might be expected from the reduction of sodium and the general picture of dilution, there was a tendency to metabolic acidosis as reflected in the CO_2 combining power.

The least reduction in sodium and chloride values occurred in No. 15 in whom the sodium was 133 meq. per liter. One might, in fact, question the diagnosis in this case. However, the fact that the convulsion occurred while intravenous fluid was running and that prompt recovery was effected by the administration of sodium chloride would appear to justify the classification of this case with the others.

Hematologic Data.—The total blood eosinophil counts in those patients in whom they were determined are also shown in Table II. In most cases the counts were low as would be expected in the normal individual shortly after surgery. In only one instance was the eosinophil value high enough to raise the question of adrenal insufficiency. This was No. 8 in whom it happened that a preoperative value had been obtained. At the time of the seizure on the second postoperative day the value was the same as before operation. This, in our experience, is a very unusual finding for patients undergoing major surgery and suggests that some degree of adrenal failure may have been responsible for the degree of electrolyte dilution which took place. In those individuals in whom epinephrine-eosinophil tests were made for pituitary and adrenal reserve, satisfactory responses were obtained (45 per cent or greater).

Although a mild leukocytosis was observed, it did not exceed that which might otherwise be anticipated in the early postsurgical period.

TABLE II. LABORATORY DATA—POSTOPERATIVE WATER INTOXICATION

CASE NO.	PATIENT	CO_2 COMBINING POWER (MEQ./1)	SERUM CHLORIDE (MEQ./1)	SERUM SODIUM (MEQ./1)	SERUM POTASSIUM (MEQ./1)	BLOOD UREA NITROGEN (MG./100 C.C.)	BLOOD SUGAR (MG./100 C.C.)	WHITE BLOOD COUNT	EOSINOPHILS PER CU. MM.
1	M. M.	26	74						
		20	66						
2	G. B.	30	80						
		32	68	108	2.2	18		17,400	
3	E. T.	22	77			10		20,700	
4	J. S.	15	78	126	5.5	40		18,450	
5	J. J.	17	83	113	3.9	7	92	14,900	
6	A. L.	27	92						
		22	80	122		16			
7	M. H.	27	79			11	106	19,000	
8	F. C.	38	74	118	3.9				93
									Same as preop.
9	B. B.	24	81			11		11,300	
10	M. H.	15	85			10	167	9,900	0; 60% response to epinephrine
11	E. W.	18	74	113	4.3	14	160	8,750	7
12	B. S.	19	83	125	5	66	94		61
13	H. H.	28	53	94	3.1	9		19,350	10
14	I. F.	17	76	114	3.7	18			12; 58% response to epinephrine
15	L. W.	24	95	133	3.2	9			2
16	R. G.	20	83	116	3.1	9			7; 45% response to epinephrine
17	A. O.	16	85	120	3.6				

Fluid Balance and Weight Change.—The intake and output data and changes in the body weight preceding the advent of convulsions are illustrated in Table III. Limitations of space make it impossible in this table to set down the figures on intake and output except for the 24 hour period which preceded the first convulsion. The change in body weight, however, is a good index of the change in state of hydration over the short periods which are involved here. In most instances (14 of the 18 cases), positive fluid balances were evidenced by a gain in the body weight. In some of these the weight increment was appallingly great: for example, No. 13, who gained 11 per cent of her normal weight in a 6 day period and Nos. 6, 14, and 16 who gained 8 per cent, 8.5 per cent, and 6.5 per cent respectively in 2 day periods.

Five of the patients (Nos. 1, 6, 14, 16, and 17) received more than 4,000 c.c. of salt-free fluid during the 24 hours before convulsions. In general, these amounts represented frank errors involving duplication of fluid orders and mistakes of a similar nature. In the majority, however, extraordinarily large amounts of fluid were not administered and in three instances 3,000 c.c or less were adequate to produce the clinical picture.

"Extracellular Space."—In addition to the two cases mentioned in the report of Ariel and associates[2] (Nos. 5 and 6) concerning the thiocyanate space

TABLE III. FLUID BALANCE DATA—POSTOPERATIVE WATER INTOXICATION

TABLE III. FLUID BALANCE DATA—POSTOPERATIVE WATER INTOXICATION

CASE NO.	PATIENT	BODY WEIGHT (IN KG.)	WEIGHT OF SURGICAL SPECIMEN (IN KG.)	WEIGHT CHANGE FROM PRE-OP. (IN KG.)	FLUID THERAPY 24 HR. PRIOR TO SEIZURE	URINE OUTPUT 24 HR. PRIOR TO SEIZURE	URINE CHLORIDE MEQ/1	FLUID THERAPY FOLLOWING SEIZURE	DURATION OF ABNORMAL CHEMISTRIES
1	M. M.	58.2	.835	+1.5	4,075 c.c. 5% & 10% glucose	475	41.5	2,000 to 3,800 c.c. 5%, 10%, & 20% gl. without NaCl daily	10 days
2	G. B.	60	1.53	+1.1	3,500 c.c. 5% gl.	1,000	142	3,000 to 5,000 c.c. 5% gl. daily with 4.5 to 9 Gm. NaCl	10 days
3	E. T.	50.5	1.120	+2.5	3,450 c.c. 5% gl.	650	12.4	3,200 c.c. 5% gl.	Patient died
4	J. S.	54.6	.285	0	3,500 c.c. 5% gl.	600	10.7	3,500 c.c. 5% gl. with about 15 Gm. NaCl and 1 Gm. KCl daily	3 days
5	J. J.			+1.3	3,500 c.c. 5% gl.	1 200	57	Fluids limited to 2,000 c.c. daily without NaCl	6 days
6	A. L.	40.0	.135	+3.2	4,200 c.c. 5% gl.	975	80	Fluids limited to 1,500 c.c. daily 13.5 Gm. NaCl on 2nd day after seizure	6 days
7	M. H.	56.8		0	3,500 c.c. 5% gl.	750		2,500 c.c. 5% gl. with 18 Gm. NaCl	2 days
8	F. C.	47	.185	−1	3,675 c.c. 5% gl. with 4.5 Gm. NaCl	1,475	2.6	3,500 c.c. 5% gl. with 13.5 Gm. NaCl	4 days
9	B. B.	58.0		+1.0	3,900 c.c. 5% gl.	1,100	60.2	3,000 c.c. daily with 9 to 13.5 Gm. NaCl	4 days
10	M. H.	43		+1.5	3,500 c.c. 5% gl.	400		1,500 c.c. 5% gl. with 13.5 Gm. NaCl	1 day
11	E. W.	58.3		+2.5	3,500 c.c. 5% gl.	1,500	164	3,000 to 3,500 c.c. 5% & 20% gl. with 9 to 18 Gm. NaCl. 50 mg. cortisone every 4 hr.	5 days
12	B. S.	49.2		+4.5	2,500 c.c.	450	6	1,000 c.c. with 9 mg. NaCl	2 days; patient died of uremia 3 wk. later
13	H. H.	53.8		+6 in 8 days	1,500 to 3,000 c.c. 5% gl. without NaCl	800 (av.)	34-98	2% NaCl	Na & Cl. elevated by therapy, but never reached normal, patient died
14	I. F.	45.4		+3.8	5,200 c.c. 5% gl.	1,650	4 25	27 Gm. 2% NaCl 1,800 c.c. fluid	12 hr.
15	L. W.	55.6	.220	+1.4	3,000 c.c 5% gl.	1,600	5	1,500 c.c. 5% gl. with 9 Gm. NaCl	1 day
16	R. G.	55		+3.6	5,200 c.c. 5% gl.	1,000	99	2% NaCl 23 Gm., later: 5% gl. to total 3,400	1 to 2 days
17	A. O.	52.2	.185	+1	4,500 c.c. with 9 Gm. NaCl	3,400	20	1,500 c.c. with 4.5 Gm. NaCl	2 days, patient died 5 days later

in surgical patients, blood volume and thiocyanate space determinations were done on two of the later patients. The finding of an enlarged thiocyanate space was confirmed in these two instances (No. 4:22,000 c.c. and No. 11:22,400 c.c. with blood volume of 3,700 c.c. and 3,100 c.c., respectively).

Results of Therapy.—No conclusions can be reached from the relationship of the type of therapy which was employed in these cases to the clinical course or final outcome. It was clearly observed, however, that in those cases which were handled by prompt administration of sodium chloride with restriction of total fluid intake there resulted a rapid improvement in the blood-chemical picture of dilution. Reversal of the electrolyte picture was much slower where this procedure was not used (Table III). Diuresis also resulted from the administration of salt. The basis for therapy in these individuals will be discussed below.

DISCUSSION

It is apparent both from the work on experimental water intoxication and from the observations on surgical patients that a number of factors are involved in the pathogenesis of convulsive seizures from extracellular dilution. These include not only the state of water balance, but also the availability of extracellular electrolytes as well as metabolic changes which are peculiar to the postsurgical individual. The rationale of prevention and therapy follows from these considerations.

Interrelationship Between Water Excess and the Availability of Salt.—The early experimental work on water intoxication demonstrated that the dilution of extracellular crystalloids was the critical factor involved in the genesis of seizures from water excess.[17, 49, 51] This holds for the situation in the human being, for although the patients in this series manifested a considerable excess of fluid intake over output, and in most instances, increase in body weight, the most characteristic finding was a reduction in the plasma levels of sodium and chloride.* Great excesses of water, if given simultaneously with their physiologic quotas of sodium chloride, will cause edema but will never produce the syndrome of water intoxication. Solutes to which cell membranes are considered to be freely permeable, however, do not share with the electrolytes the ability to prevent the disturbance resulting from excess water. This has been demonstrated experimentally for urea and glucose and is apparent from clinical experiences exemplified by the present series in which 5 per cent glucose was the usual solution used for water administration.[15, 19]

One aspect of the physiologic consequences of lowering the serum electrolyte concentrations has particular significance with regard to perpetuating a state of hydremia. It has been repeatedly shown that diminution of the serum sodium level produces a decrease in glomerular filtration and in the diuretic response to a water load.[24, 55] This has been quantitatively studied in the recent work of Bristol in which a definite correlation between the serum sodium level

*While a medical house officer at the University Hospitals in 1922-23, one of us (O.H.W.) saw convulsions in patients with hypertension who had been on a restricted intake of sodium chloride (less than 2 Gm. per day), following the ingestion of 1,500 c.c. of water over a 10 minute interval (Volhard Water test of kidney function). These were undoubtedly instances of water intoxication, abetted by the low salt intake.

and urine output following a water test was demonstrated.[5] Similarly Ariel and Miller found glomerular filtration and renal plasma flow to be reduced in hypochloremic human patients and subjects.[3] It is apparent that a self-perpetuating cycle of dilution—failure of diuresis—dilution is possible. The therapeutic implications of this relationship between sodium level and renal function are discussed later.

Susceptibility of the Surgical Patient.—Seizures were seen only in postoperative patients, although other patients frequently receive parenteral fluids, and they were confined to a 2 day interval subsequent to the operation. There are some clinical and experimental observations which help to explain this remarkably high incidence in a short segment of the postoperative period.

During the first 24 hours after surgery, sodium and chloride concentrations regularly fall from the preoperative levels.[1, 6, 33] The postoperative depression of chloride, in particular, has been recognized by surgeons for many years.[28] This depression of the major extracellular electrolytes is always observed even in the absence of any abnormal electrolyte losses and occurs despite the sharp limitations of renal sodium and chloride loss which normally occurs following operation. In our findings, the electrolyte concentrations remained depressed for 4 to 6 days following standard operations and the levels to which sodium and chloride dropped were lower following very extensive operations than were reached after smaller or standard procedures.[57] The relatively dilute state of the extracellular ions in the postsurgical patients is related to an expansion of the thiocyanate space.[31] From these observations it can be concluded either that the extracellular space becomes larger or that anomalies of permeability result in the assumption by these ions of an abnormal position in relationship to the fluid boundaries. Methods which have been applied to the problem to date do not permit this distinction to be made. Relative oliguria is also considered characteristic of the early postoperative period. The nature of postoperative oliguria and intolerance to water has recently been studied in detail by Moyer.[40]

This pattern of changes in fluid and electrolyte distribution in the individual who has undergone surgery finds its counterpart in the observations which have been made on animals following exposure to nonspecific stress. Selye, in his early work on the "adaptation syndrome," found blood chloride levels to be severely depressed during the "shock phase" of the syndrome.[48] They returned to normal or became elevated during the subsequent "countershock" and "resistance" phases. Similarly, Howlett and Browne found that oliguria and over-all retention of water were characteristic of the "shock phase" as were abnormalities of membrane permeability which resulted in edema formation and accumulation of fluid in the serous cavities.[25] During the "countershock" and "resistance" phases, diuresis occurs with mobilization of abnormally located fluid and resulting elevation of the extracellular ionic concentrations. The latter turn of events is believed to be made possible by the appearance of large amounts of adrenal steroids. Adrenalectomized animals display a much

greater tendency to water retention and edema following trauma; hypochloremia is more profound and the hyperchloremic phase of the electrolyte response is much less in evidence.

The phenomena of water retention and dilution which occur in the postoperative patients and which have their analogues in the "shock phase" of the traumatized experimental animal are not clearly understood. A great deal of investigation remains to be done on the possible renal, endocrine, nervous, and hemodynamic influences which may mediate this early portion of the response to trauma. The intolerance to water and the susceptibility to water intoxication during the immediate postsrugical phase are assuredly manifestations of these same phenomena.

A further quality which water intoxication shares with the deleterious effects of stress is the antagonistic effect upon it of adrenal hormones. This extremely interesting relationship between susceptibility to water intoxication and adrenal function has been extensively reviewed in the works of Gaunt and his colleagues.[13, 14] Whereas adrenalectomized animals are extremely sensitive to the injurious effects of water excess, it is possible by the use of adrenal substances to render normal animals almost completely refractory to water intoxication.[11, 12, 50] Similar effects in the human being have been observed by McQuarrie.[36, 56]

The important position of the adrenal hormones in regard to resistance and susceptibility to water intoxication raises the question of whether a degree of adrenal insufficiency could be responsible for the development of seizures in some of these individuals. Such a mechanism might be considered particularly in those cases in which very great excesses of fluid were not involved. It was for this reason that eosinophil counts were done on a number of these people at the time when convulsions were observed. As was mentioned above, in only one instance were the circulating eosinophils high enough to suggest the possibility of adrenal insufficiency. It must be appreciated, however, that the depression of eosinophil count consequent to surgery is an extremely sensitive index of adrenal activity. The possibility that a relative inadequacy of adrenal response to operative stress may play a role in the abnormal tendency to hydremia cannot at present be excluded. In the one case in which the postoperative eosinophil count was found to be the same as the preoperative level, it seems highly probable that such a mechanism was contributory.

Mechanism of the Cerebral Disturbance.—Sodium and chloride, to which cell membranes are believed to be relatively impermeable, readily protect the organism from the symptoms of water intoxication. Since this protection is not afforded by freely diffusible solutes such as urea and glucose, it is believed that the mechanism of the cerebral disturbance in water intoxication is an intracellular edema resulting from migration of water from the diluted extracellular fluid to the interior of the cell.[13] This is the currently accepted scheme which seems to satisfy the experimental observations.

Contrasting Effects of Hyperconcentration and Hypoconcentration of Extracellular Electrolytes.—As would be expected, severe central nervous system disturbance can also result from hyperconcentration of the major extracellular

electrolytes.[30] This situation has been observed clinically under various circumstances and was recently brought to our attention in a series of surgical patients who developed severe hypernatremia and hyperchloremia without dehydration in the usual sense.[58] The immediate mechanism of damage to nervous tissue in these instances appears to be a movement of intracellular fluid to the extracellular compartment in the process of equilibration which follows an increase in osmolarity of the extracellular fluid. The effects of the cellular dehydration which results are functional changes which differ strikingly from those of cellular overhydration. Whereas seizures characterize the syndrome of water intoxication, profound central nervous system depression is the most constant finding in the group with elevated electrolytes. The latter patients in some instances exhibit purposeless and athetoid movements suggesting depression of higher integrating centers. Whereas in water intoxication, especially as seen experimentally, hypothermia and hypertension are regularly observed, severe hyperpyrexia presumably of central origin and shock are characteristic of the hyperconcentrated group.

Therapy and Prevention of Water Intoxication.—A variety of therapeutic regimes were employed in these patients. In the earlier cases the nature of the seizures was not always immediately recognized and appropriate measures not instituted as rapidly as desirable. The great variations in gravity of the clinical pictures make it impossible to evaluate the therapy on the basis of clinical course. It is clear, however, that in severe cases the correction of water balance and the return of the electrolyte levels to normal can be expeditiously achieved only by the administration of salt as soon as the diagnosis is made and by rigorously limiting the total fluid intake. In most instances this can only be accomplished by the use of hypertonic salt solution. We have used 2 per cent saline solution, starting with the administration of 18 to 27 Gm. of salt in this concentration. Salt-free glucose solution should not be given before the sodium has risen to reasonable levels and an adequate diuresis is demonstrable.

Fig. 2 illustrates the depressed blood chemistries, positive water balance, and weight gain which had occurred in a typical patient (No. 14) 36 hours after operation. It shows also the immediately satisfactory result which was obtained by administration of 2 per cent saline solution. This treatment effected a prompt increase in serum sodium, chloride, and bicarbonate levels as shown by the next set of determinations which were carried out 8 hours after the first saline infusion. The concentrations subsequently continued to rise, and diuresis and gradual weight loss ensued. In cases where salt was not given immediately and in substantial amounts, several days were frequently required for the sodium and chloride levels to return to normal. In view of the experimental findings mentioned above in which hyponatremia was related to renal impairment and failure of water diuresis, it would seem highly desirable to raise the sodium level as rapidly as possible. The frequent occurrence of diuresis following restoration of the sodium and chloride concentrations has confirmed the validity of this approach.

Most cases of water intoxication could be prevented. It is necessary only to realize that the patient is extremely sensitive to water excess for 48 hours after

surgery and to give no more water than is necessary to cover predictable fluid losses and assure adequate urinary output. Because of the work of Jones and Eaton[26] and of Coller and his co-workers[7, 8] pointing out the dangers of sodium chloride solution in the postoperative patient, it has been the custom of many surgeons to give no salt during the first 24 hours after operation. We now feel, however, that it may be wiser to give small amounts of salt (4.5 to 9 Gm.) on the day after surgery, thereby avoiding a 2-day period during which the patient may receive considerable amounts of salt-free glucose solution at a time when he is least able to tolerate it.

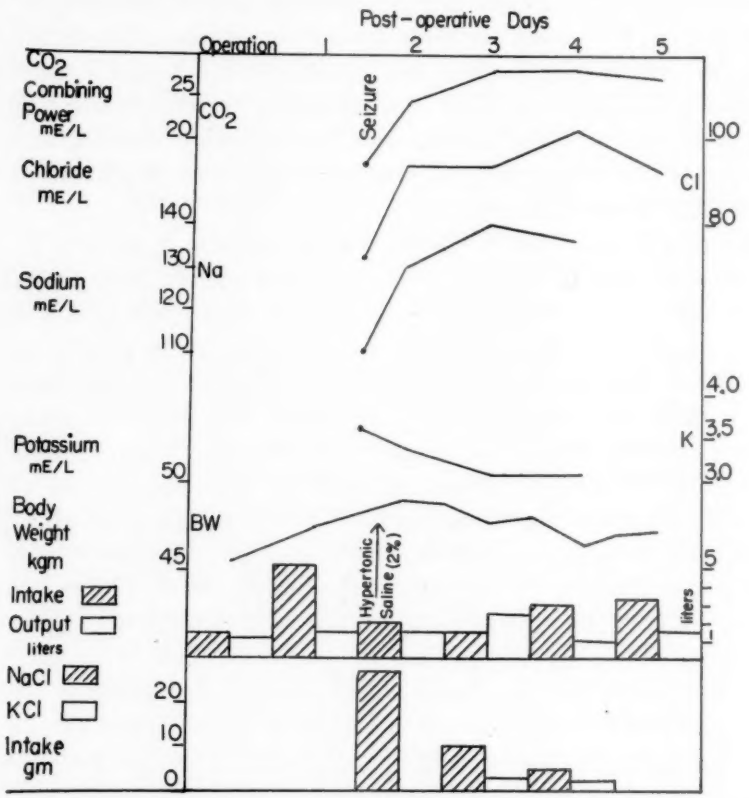

Fig. 2.—Fluid balance. Body weight and serum electrolyte levels in patient No. 14 at time of seizures and following institution of therapy (see text).

Serum sodium and chloride levels fall following all operations. It has been our experience that after very extensive and prolonged operations these concentrations drop more precipitiously and not infrequently approach the levels at which seizures are seen.[57] It would seem reasonable, in connection with some of these large operations, to follow the sodium level during the first two or three postoperative days, thereby prevising possible difficulties of this nature and preventing them by appropriate administration of salt or limitation of parenteral glucose solution.

Finally, in the prevention of electrolyte complications of this sort, there is no substitute for careful surgery, minimizing of blood loss, and adequate blood

replacement. A long operation in which blood volume is not replaced save by a continuous drip of glucose solutions sets the stage for the development of water intoxication. To allow this to happen is to invite results as dire as those which were attributed to the methods of Lesage's Doctor Sangdrado who treated all his patients by phlebotomy followed by the administration of prodigious quantities of water.[29]

SUMMARY

Seventeen instances of convulsive seizures following surgical operations and characterized by dilution of the extracellular electrolytes are reported. In all but one of these the convulsions occurred between 12 and 48 hours after the operation. In most instances, strongly positive fluid balance was demonstrable by the intake and output data and the change in body weight. The mechanisms of water intoxication are discussed in the light of previously reported experimental findings and the physiologic peculiarities of the postoperative patient.

It is concluded that most complications of this nature could be prevented by the avoidance of excessive amounts of glucose solution at the time of surgery and through the days immediately following surgery. Daily estimations of the body weight and determinations of serum electrolyte levels before actual disturbances develop should make it possible to take measures to prevent this complication before it occurs. Hypertonic saline solution has been of great value in rapidly restoring the normal salt-water relationship of the extacellular fluid once seizures have occurred.

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THE OPERATIVE REMOVAL OF TUMORS OF THE PAROTID SALIVARY GLAND

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IN THE surgical removal of parotid tumors there are at least two cardinal principles: first, the tumor must be completely removed, and second, unnecessary injury (either temporary or permanent) to the seventh cranial nerve or its larger branches must be avoided whenever possible. Although it is well known that complete paralysis of the facial nerve is compatible with health, nevertheless, the resultant deformity of one side of the face, frequently associated with epiphora or corneal ulceration, is a tragic complication, both somatic and psychologic. For this reason, in his concern to avoid such injury to the seventh nerve, the surgeon who lacks sufficient knowledge of the anatomy of the parotid gland and surgical experience in this region often proceeds with undue timidity and caution. Such an inhibited approach on the part of the surgeon commonly results in an entirely inadequate operation which fails to remove the tumor completely. The frequency with which such incomplete operations are performed can be illustrated by the results of the survey of the clinical material observed. In the Head and Neck Clinic in Memorial Hospital it is found that 36 per cent of all patients admitted for the treatment of parotid tumors have had one or more previous operations for attempted removal of the growths.

The complete removal of the parotid gland with sacrifice of the facial nerve is an old procedure[6] and admittedly is capable of permanent control of the local disease in most cases; nevertheless, in actual practice most surgeons would be loathe to carry out such a drastic operation except where most of the gland is found to be invaded by cancer. For the majority of parotid tumors, either benign or malignant, the ideal surgical program would be one designed to remove the tumor together with a portion of the parotid gland and to spare all or whatever branches of the nerve are uninvolved by the growth. Over the past quarter century there has been a steady systematic evolution of such a conservative surgical procedure.

The tendency in recent years, however, has been to advocate an extracapsular enucleation of the tumor. While this limited type of operation may be successful for the smaller encapsulated growths located in the superficial or peripheral portions of the gland, nevertheless, it seldom proves to be adequate for the larger growths. For example, a tumor which on clinical examination appears to be located in the superficial portions of the gland is frequently found at actual operation to extend into the deeper portions of the organ or to be infiltrating rather than encapsulated. In other words, it is difficult in many cases

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to predict the surgical anatomy of a given parotid tumor, and often the situation at operation turns out to be more complicated than was suspected clinically. The histories and initial clinical examinations of many patients with residual parotid tumors suggest that the surgeon was of the opinion at first that the growth was superficial and could be removed easily, either in his office or in the hospital, by a limited incision under local anesthesia. At the time of the operation, however, the surgeon had become confused, had lost confidence, and had "backed out" after an ineffectual attempt to remove the mass. In many of these cases it is plain that the tumor was cut into and fragments spilled and implanted throughout the wound, since the recurrences take the form of multiple (sometimes 15 or 20) separate and diffusely distributed nodules (seeding of the gland).

In recent years reports have been published on the surgery of the parotid gland in which the operative techniques are based upon a more thorough knowledge of the anatomy of the seventh nerve in the parotid gland and the principle that if the nerve is to spared, it must first be exposed and identified. Some have advocated identification of a peripheral branch somewhere along the anterior border of the gland in the cheek and following the branch centrally so as to discover the larger branches and finally, if necessary, the main trunk of the seventh nerve.[7, 8] Such a maneuver, although successful in some cases, will be found unworkable for larger tumors. Furthermore, this technique, even though successful, is actually the "hard way" and an unnecessary expenditure of effort. In the Head and Neck Clinic at Memorial Hospital it has been found that an immediate and direct approach to the main nerve just after it emerges from the stylomastoid foramen to enter the parotid gland is a sounder and more workable procedure. Any further discussion of the rationale of such an approach must be based upon an understanding of the surgical anatomy of the seventh nerve.

SURGICAL ANATOMY OF THE SEVENTH NERVE

The facial nerve emerges from the stylomastoid foramen, passes downward, forward, and outward for a distance varying from 0.5 to 1.5 cm. and then dips into the posterior aspect of the parotid gland. Shortly thereafter, the nerve divides into two main trunks (temporofacial and cervicofacial divisions), but occasionally the bifurcation may occur before the nerve enters the gland. After the two major branches have traversed the gland for a distance varying from 0.5 to 1 cm., subdivision occurs with the formation of a nerve network—numerous intercommunications forming the actual plexus.

Elaborate descriptions have appeared in the literature[1, 5] which purport to show that the seventh cranial nerve does not pierce the true capsule of the parotid gland, but that in its division the two main trunks surround and indent the gland which is alleged to be dumbbell or collar-button shaped. On the basis of this anatomic relationship, it is claimed that the parotid gland can be removed more readily than if, as formerly believed, the nerve actually passes through the gland. Such a contention may be basically true from the standpoint of developmental anatomy; nevertheless, when the nerve invaginates the

capsule and the salivary gland tissue, it actually lies within the parotid gland from the standpoint of applied surgical anatomy.[3, 4] (Figs. 1 and 2.) Therefore, from a practical point of view, the above mentioned anatomical concept is of academic significance only. At the time of operation the surgeon is faced with the fact that *from the standpoint of surgical anatomy the seventh nerve lies within the parotid gland for a considerable portion of its course, and the maneuvers of the surgeon must be based upon this premise if injury to the nerve is to be avoided.*

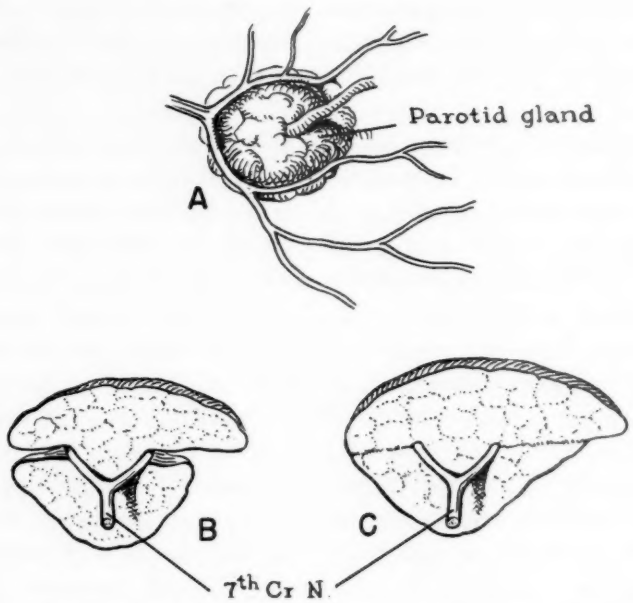

Fig. 1.—Embryologically the parotid salivary gland arises in the crotch (*A*) where the seventh nerve first divides into the temporofacial and cervicofacial divisions. As the gland develops it folds over the nerve (*B*), and finally, these overlapped portions of the gland fuse (*C*) so that for all practical purposes the seventh nerve comes to lie *within the gland* for a considerable portion of its course.

OPERATIVE TECHNIQUE

Whether or not a given parotid tumor may be safely enucleated by sharp and blunt dissection along its capsule, or whether a margin of normal parotid gland must be included in the resection, will depend upon the morbid anatomy in the given case. For example, certain parotid tumors of long duration are firm, cartilaginous in consistency, and encapsulated; and during their slow progressive growth they have become extruded and lie mostly outside the substance of the parotid gland itself. It is surely unnecessary to remove such growths with a wide margin of normal salivary gland tissue. At the other extreme will be found definitely infiltrating tumors, the actual extent of which cannot be determined at the time of operation. In these cases, consideration should be given to excising all or most of the gland, sacrificing some of the major branches or even the main nerve if necessary. The operative technique is shown in the accompanying illustrations. The following discussion will not include many of the specific details which are shown graphically in the illustrations and in the appended legends.

Form of Incision.—A satisfactory incision for the adequate exposure of all parts of the parotid gland is the Y incision shown in Fig. 3; an anterior extension may be employed for the more extensive tumors. The Y incision permits upward retraction of the ear and access to the posterior and retromandibular portions of the gland. The incision is so located that after complete healing has occurred the cosmetic result is acceptable. It may be used in practically all cases, except for small, well-encapsulated tumors at the anterior edge of the gland. In the latter instances, a small incision made directly over the mass itself will often suffice. (See Fig. 10.)

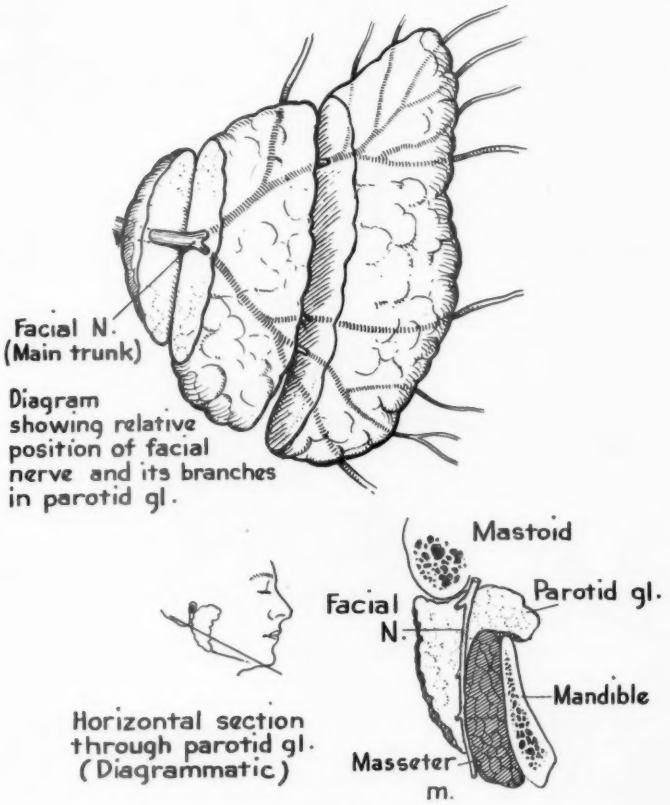

Fig. 2.

Development of Skin Flaps.—In dissecting back the skin flaps, the cleavage plane should be along the capsule of the parotid gland which is thin and somewhat difficult to follow, especially in a highly vascular field. In any case, the dissection should at no time approach too closely to the actual tumor. There is no danger in developing cutaneous flaps as described above, for the seventh nerve plexus lies deep within the gland itself. Even if the superficial portions of the gland are cut into and small nodules left behind, no fear need be entertained that postoperative salivary cysts or fistulas will develop from the remaining glandular fragments. As a matter of fact, considerable portions (up to 1 to 1.5 cm. in diameter) of the periphery of the gland may be left without fear of

complications provided the central portions of the gland containing the larger ducts are excised.

The anterior or cheek flap is dissected forward exposing the central portion of the gland. The posterior flap is dissected backward toward the mastoid bone and adjacent sternomastoid muscle, exposing the tail of the gland. By dissecting the lobule of the ear and the posterior wall of the cartilaginous external auditory canal upward, the upper limits of the gland are reached.

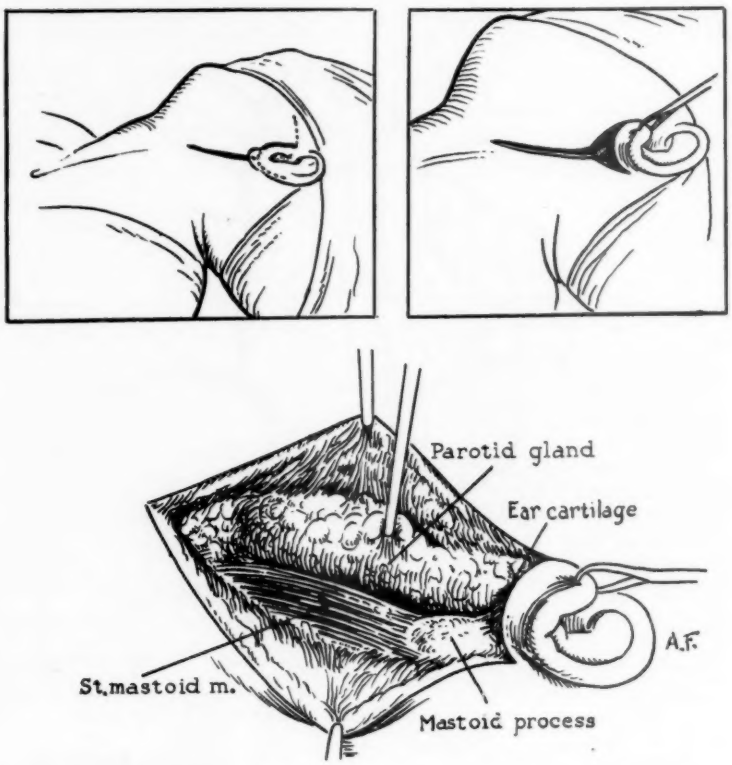

Fig. 3.—A Y-shaped incision is made with the upper arms extending anteriorly and posteriorly to the ear; the lower arm of the incision is slightly curved and extends downward into the neck. An anterior extension along the lower border of the zygoma is optional. The skin flaps are dissected off the parotid anteriorly and off the mastoid process and sternomastoid muscle posteriorly. The ear is reflected upward by sharp dissection.

Exposure of the Main Trunk of the Facial Nerve.—If the main trunk of the seventh nerve is exposed in all cases, the chance of inadvertent injury to this vital structure is practically nil. The logic of this surgical principle has been emphasized in thyroid surgery by Lahey, where, by routinely exposing and identifying the recurrent laryngeal nerve it may be preserved in all cases when not actually invaded by a growth. It is only by exposure and identification of important structures that injury to them can be avoided with certainty.[2] In most descriptions of surgical procedures hitherto proposed for the removal of parotid tumors, the authors have advised that the facial nerve can readily and safely be located by identifying one of the terminal branches and then dissecting backward to demonstrate the main nerve trunk as it emerges from

the stylomastoid foramen. Such a procedure is both tedious and hazardous, especially where there has been distortion of the facial nerve plexus by bulky or infiltrating tumors or by scarring due to previous surgical procedures or radiation therapy. The maneuver of exposing the main nerve trunk initially (posterior approach) is often regarded as difficult and time consuming. Experience has shown, however, such is not the case. Once the skin flaps have been developed, the exposure of the main trunk of the nerve at a point where it emerges from the stylomastoid foramen should not take the experienced surgeon more than five minutes (often less). Such experience is best obtained by first assisting at several operations and/or by at least one cadaver dissection made for this specific purpose. A thorough knowledge of the anatomy of the region will convince the surgeon that the position of the nerve is constant at this point.

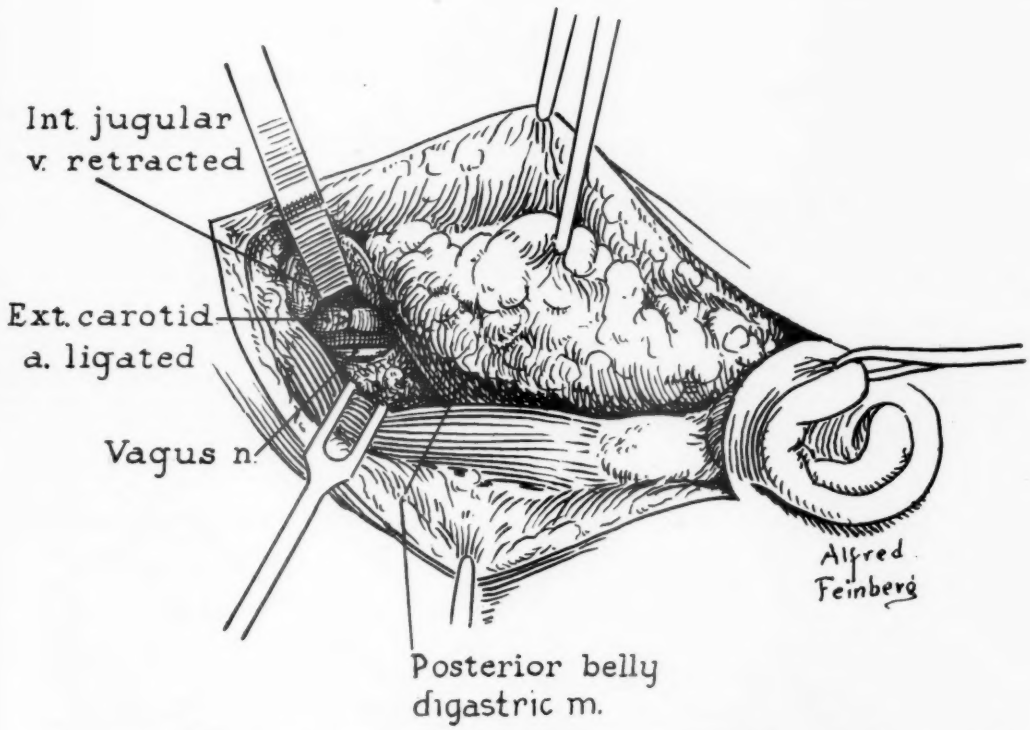

Fig. 4.—Ligation of the external carotid artery is optional. It is sometimes indicated in cases of bulky, highly vascular tumors. For the average case it is not necessary and may even be objectionable, since it produces scarring in the field of a neck dissection should the latter operation be indicated later. The external carotid artery may be exposed just beneath the posterior belly of the digastric muscle.

Exposure of the upper border of the posterior belly of the digastric muscle and its attachment to the mastoid process will serve as an important landmark. Just above the attachment of this muscle a potential space is entered through which passes the main trunk of the seventh nerve after it has emerged from the stylomastoid foramen. The main nerve trunk when first seen is between 3 and 4 mm. in diameter and is readily identified. The less experienced surgeon may often fear that during the dissection to a depth of about 1.5 cm. the nerve may

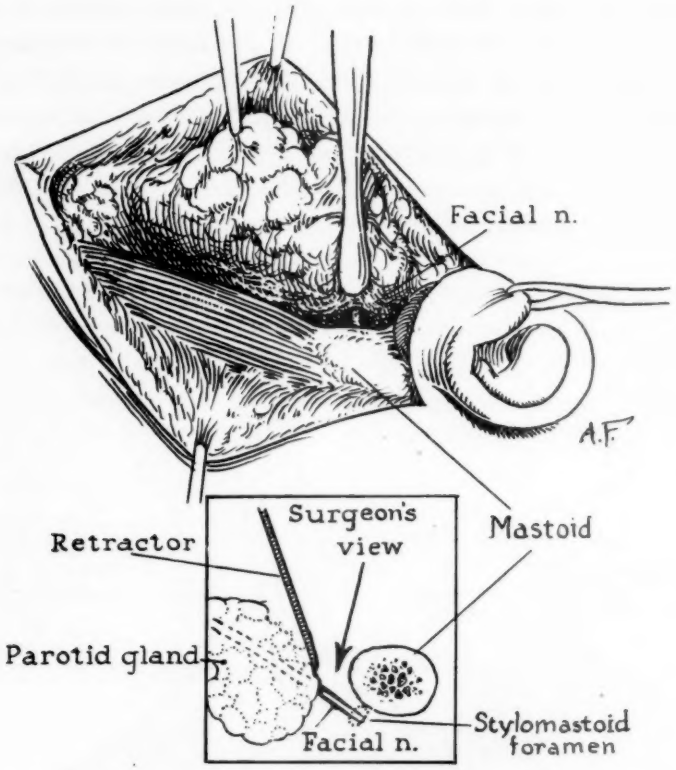

Fig. 5.—The main trunk of the facial nerve is exposed at a depth of about 1.5 cm. from the external surface of the mas oid process by dissecting directly downward along the anterior border of the mastoid process above the attachment of the posterior belly of the digastric muscle. The exposure is made by blunt dissection along the posterior capsule of the parotid, pushing the gland an eriorly. The main trunk of the seventh nerve is usually found at a depth of about 1.5 cm. from the outer surface of the mastoid.

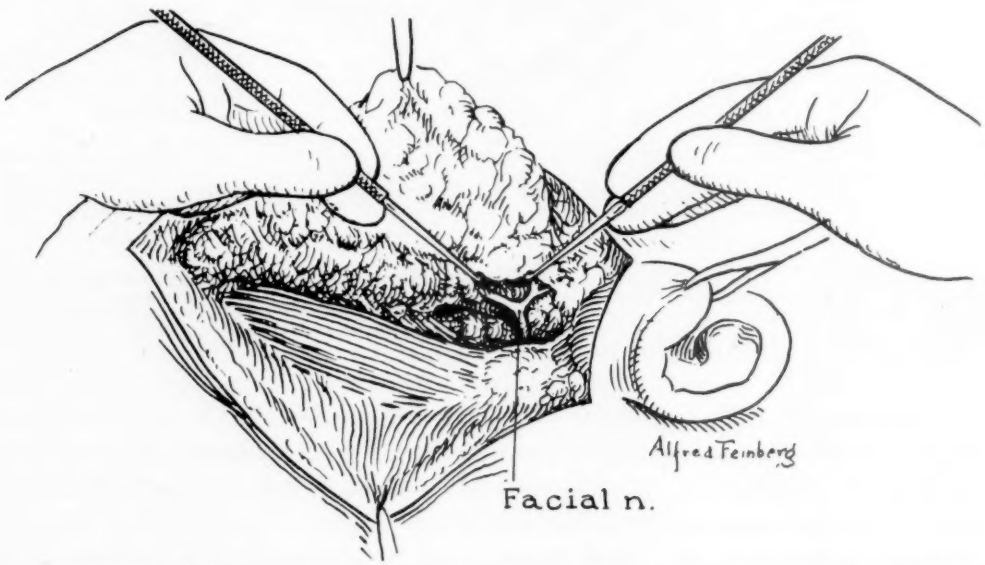

Fig. 6.—As the dissection proceeds along the main seventh nerve, the bifurcation is reached (temporofacial and cervicofacial divisions). Occasionally the bifurcation of the nerve may occur before it enters the posterior aspect of the parotid gland. A nerve branch is being isolated from the gland tissue by pointed dissectors.

have been accidentally severed, but no fear need be entered if the dissection has been made with reasonable care, and the surgeon may be assured that if he goes just a little bit further the nerve will appear.

Fig. 7.—Seventh nerve dissectors, pointed probes with ends bent at right angles, are useful in dissecting out plexus of the nerve within the parotid gland.

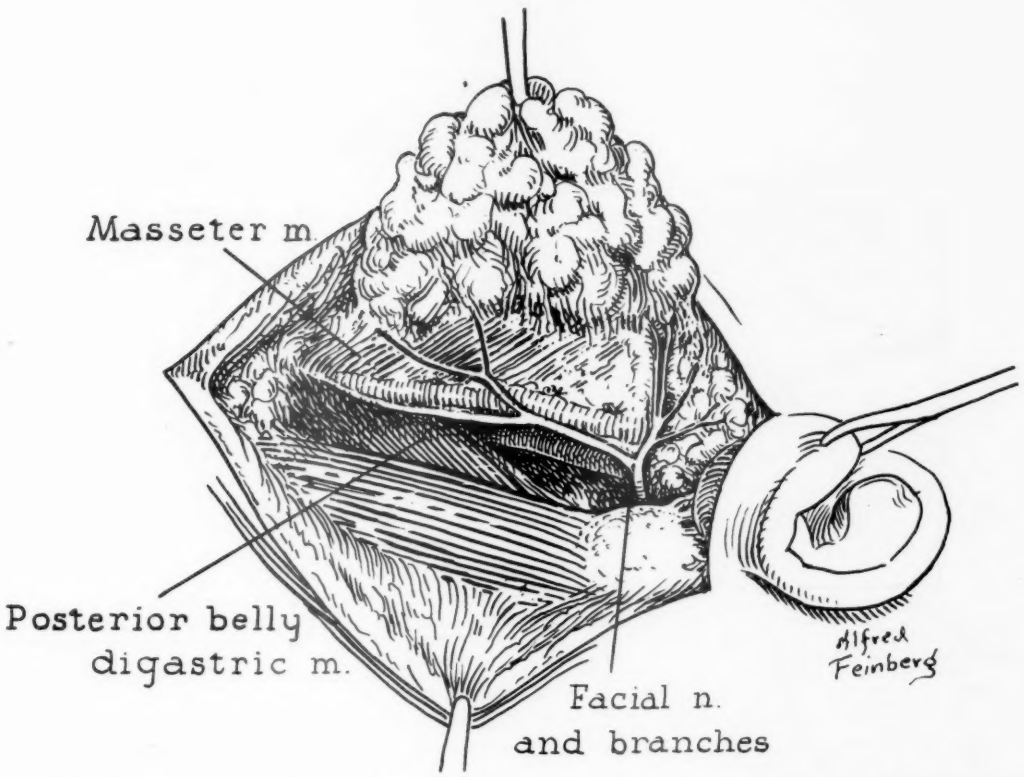

Fig. 8.—Once the main trunk of the seventh nerve has been identified, the parotid gland may be separated and pushed forward by blunt dissection, exposing and preserving all branches of the nerve. It is of particular importance to identify and preserve the *ramus marginalis mandibuli* (to the lower lip).

Resection of the Parotid Gland.—Once the main trunk of the facial nerve has been demonstrated, the parotid gland and any tumor within it may be readily dissected off under direct vision without any danger of inadvertent injury to the nerve or its major branches. The sharp, right-angle, pointed dissectors shown in Figs. 6 and 7 are useful in exposing and freeing the nerve branches as they progress through the gland. A workable temporary substitute for this instrument may be found in what has long been known in the instrument trade as the Gross combination Ear Spoon and Hook. The only possible way in which the main trunk of the nerve or a major branch may be permanently

injured is by deliberate sacrifice (elective section) when the surgeon finds that a branch runs directly through the tumor. After that portion of the parotid gland superficial to the nerve and its branches has been excised, the remnant of gland behind the nerve plexus can only be removed piecemeal. Extension of the tumor mesial to the nerve plexus often occurs.

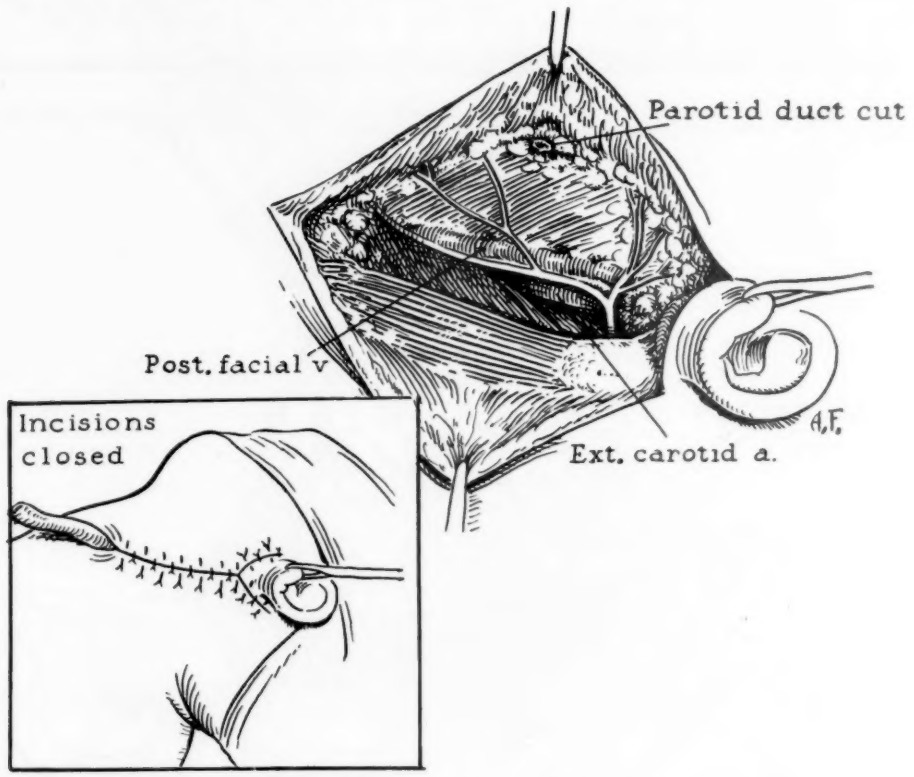

Fig. 9.—As much of the parotid gland as desired may be removed with the tumor en bloc. Peripheral fragments of parotid tissue may be left behind without fear of postoperative salivary fistula formation.

The branch of the facial nerve most liable to injury during the dissection is the *ramus marginalis mandibulae* which is usually given off from the main cervicofacial trunk but occasionally is found to arise from a common trunk with the cervical (platysmal) branch. In any case, the mandibular branch tends to be rather isolated, and apparently it has little or no anastomosis peripherally with other rami of the facial nerve. For this reason, it is advisable to carefully dissect out and preserve this particular structure. Even though many of the smaller anastomosing branches in the cheek may be sacrificed without fear of permanent facial paresis, such is not the case when the mandibular branch is cut. Permanent paresis of the homolateral half of the lower lip will inevitably follow transection of the *ramus marginalis mandibulae.*

Most parotid tumors are fairly well delimited within the gland, and if an adequate margin of normal salivary gland tissue is included in the resection, there should be little fear of local recurrence. Except in widely infiltrating tumors it is not necessary to remove every vestige of the parotid gland, but

rather, to remove that portion of the organ within which the tumor is embedded. If the growth appears to infiltrate the gland diffusely, it is obvious that the entire organ must be removed; in these cases, it is not only justifiable but mandatory that the main seventh nerve and its entire plexus be sacrificed. If only one of the peripheral branches is found to be involved by the tumor, such a structure should not be preserved. In many instances the sacrifice of one or more peripheral branches will be followed eventually by appreciable recovery of the initial paralysis (except the mandibular branch) due to terminal anastomosis.

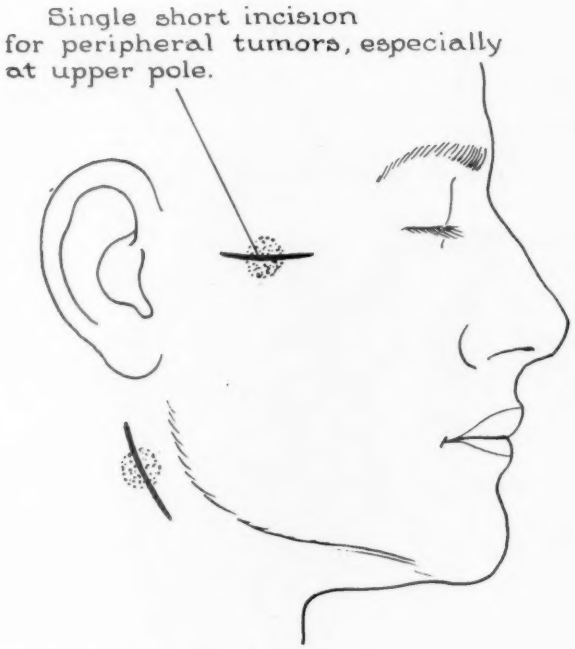

Fig. 10 (Variation in technique).—In the cases of small, superficial, sharply delimited (under 1.5 cm.) tumors located either in the extreme upper or lower poles of the parotid gland, one may be justified in using a short, straight incision directly over the growth and in performing an extracapsular enucleation, thus avoiding the more extensive operative procedure previously described.

This limited form of incision should not be used for tumors of large or even moderate size, since the inadequate exposure too often results in incomplete removal of the growth. The short incision is also risky in anteriorly placed tumors because of danger of sectioning Stenson's duct and the formation of a permanent salivary fistula. Should the removal of an anteriorly situated growth involve risk of injury to the duct, it is much safer to remove the whole parotid gland along with the anteriorly placed tumor.

Ligation of the External Carotid Artery.—The upper portion of the external carotid artery and the posterior facial vein groove the mesial surface of the parotid gland deep to the facial nerve. When the entire gland must be extirpated and the nerve sacrificed, these two vessels must naturally also be removed. In the average case of partial resection of the parotid gland, however, the vessels need not be disturbed.

The question often arises as to whether the external carotid artery should be ligated at a point below the posterior belly of the digastric muscle so as to reduce the hemorrhage in the operative field. Such ligation does minimize to some extent the amount and vigor of arterial bleeding, although much of the

bleeding during the operation is actually of venous origin and can be controlled by local clamping and pressure. After the skin flaps have been developed, the ligation of the external carotid artery is readily done, if desired, through the lower end of the incision. External carotid ligation during the course of resection of the parotid gland has this disadvantage, however: should the tumor

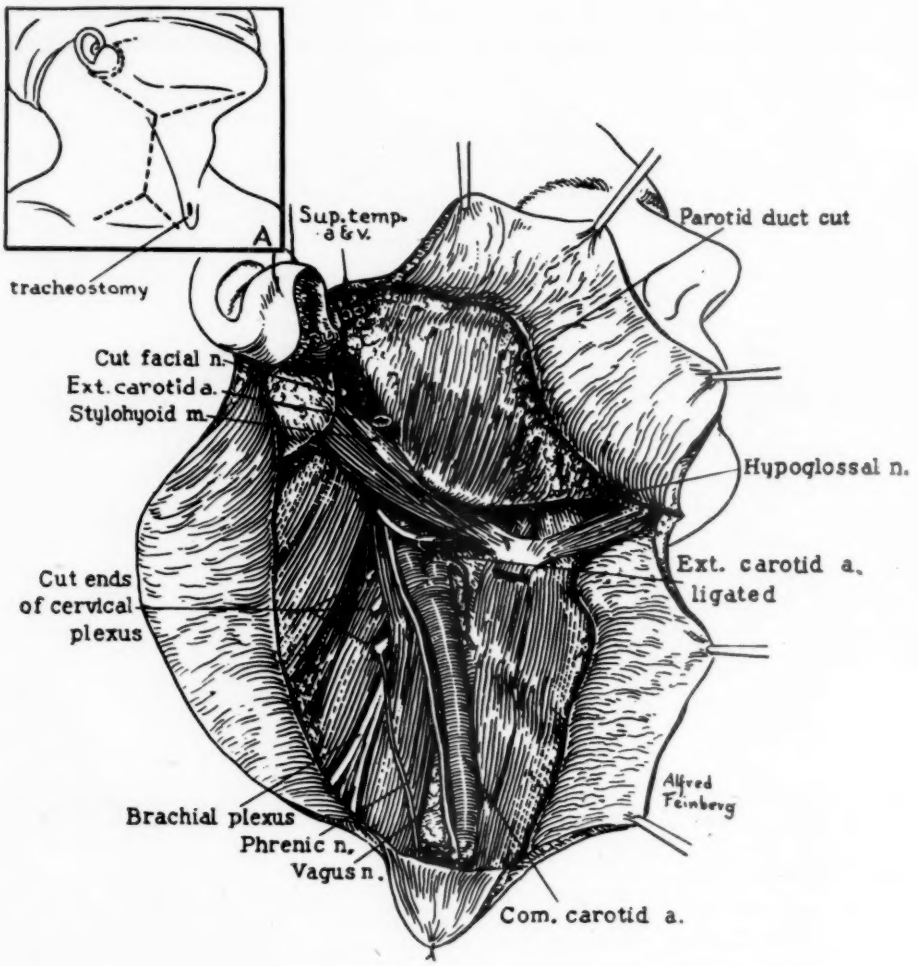

Fig. 11 (Combined neck dissection and resection of the parotid salivary gland).—When there is clinical evidence of cervical metastasis from cancer of the parotid gland, a radical neck dissection may be combined with excision of the parotid gland.

In such cases, the primary tumor is usually widely invasive, and it would be unsafe to attempt the preservation of all the branches of the seventh nerve. In such operations it is sometimes safe, however, to preserve a portion of the temporofacial division (eye).

prove to be unexpectedly malignant so that neck dissection is required at some later date, then surgical scarring in the upper neck (from the ligation) will definitely interfere with the subsequent operation—that is, neck dissection cannot be as effectively performed. Since arterial ligation is not absolutely necessary, it had probably best be omitted during routine resection of the parotid gland since there is always a possibility that neck dissection for parotid cancer may have to be done later in certain cases.

Postoperative Dressing.—In all cases the wound is drained routinely because the dissection is extensive and the operative defect large. The skin flaps are approximated to the underlying tissues snugly by the use of bulky pressure dressings. The drain is removed on the first postoperative day, and the pressure dressing replaced for an additional 24 hours.

Neck Dissection.—The operation of resection of the parotid gland may be combined with neck dissection so that the entire specimen (parotid gland, sternomastoid muscle, internal jugular vein, submaxillary salivary gland, and accompanying lymph nodes) is removed en bloc, as shown in Fig. 11.

TRANSIENT POSTOPERATIVE FACIAL NERVE PARALYSIS

Temporary facial paresis is frequently seen because of operative trauma to the seventh nerve or its branches. This is especially common after manipulation of the mandibular branch with resultant weakness of the homolateral half of the lower lip. It is frequently necessary to dissect out the mandibular branch for a distance of 3 to 3.5 cm. so this structure may undergo considerable trauma. If the surgeon knows definitely that he has not sectioned any of the major branches, he may assure the patient that the facial asymmetry will disappear in about three or four months. During the recovery period, physiotherapy (galvanic or faradic current) is useful in maintaining muscle tone, and at the same time discouraged patients are provided with a placebo.

GUSTATORY SWEATING

In approximately 5 per cent of patients who have been subjected to partial or subtotal resection of the parotid salivary gland, there is a complaint, especially after eating, that "water runs down the side of my face." The surgeon unfamiliar with this phenomenon may conclude that there is a salivary fistula. As a matter of fact such "gustatory sweating" is frequently encountered in operations involving the auriculotemporal nerve. Objectively, it takes the form of droplets of clear liquid on the skin just in front of the ear and zygomatic region. In some patients the syndrome disappears spontaneously after a few months, but in others the complications persist indefinitely although the severity tends to lessen with the passage of time. The syndrome was originally described by Lucie Frey (Revue Neurologique **2**: 97, 1923).

SUMMARY

Two cardinal principles in surgery of parotid gland tumors are: first, the complete removal of the growth, and second, avoidance of injury to the seventh nerve. The risk of injury to the facial nerve acts as a deterrent to an adequate exposure in many operations for parotid tumors with the result that many growths are incompletely removed. The best method of avoiding such injury is the routine exposure and identification of the nerve first, before proceeding with the actual removal of the tumor. The nerve can be most safely and readily exposed proximally as it emerges from the stylomastoid foramen. The form of skin incision and the operative technique for parotid tumors with preservation of the seventh nerve is described.

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WOUND HEALING AND THE STEROIDS

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THE observation that some of the steroids alter wound healing is of great interest. It has led to numerous reports in the literature on the subject. Most of these indicate that ACTH and cortisone have a definite inhibiting effect on fibroplasia and wound healing.[1-9]

We, too, fell under the spell of these drugs and likewise made an attempt to solve some of the mysteries of wound healing. Our only fault was that we came up with a different answer. At least it was partly in variance with the above reports. Because of this and our skepticism of most wound-healing studies, a report of our experiences is in order.

There are literally dozens of variables which enter into the problem of every healing wound. This is only too evident to those attempting to establish controls in any wound study. To the questionable control is added the variable which happens to be under scrutiny. Add to this the inaccuracies of determining the wound strength or degree of healing[10] and the problem becomes nebulous indeed. Fully realizing the weaknesses of all such investigations, we have chosen to study wound healing by two methods. These were by histologic study and by wound avulsion to test healing wound strength.

It seemed of particular interest to determine if the administration of the various sterols altered the latent period[11, 12] of wound healing. The ability to do this would be valuable indeed since it must be closely associated with the very basis of wound healing. This is a very tangible feature since it can be so accurately determined. The latent, or lag, period of wound healing may be defined as that time interval between tissue injury and the beginning of proliferation by fibroblasts or epithelium. It is determined on microscopic section by noting just when proliferation starts. This unexplained period of inactivity varies from two to four days for fibroblasts and somewhat longer for epithelium. What a boon to surgery it would be if the lag period could by some means be eliminated completely!

METHODS

Long-Evans Laboratory male rats weighing 145 to 360 Gm. were used as the test animals. They were fed Harlan Special Rat Ration with no additions. Some sixty animals were used and in these a total of 377 skin wounds were made in the four groups tested.

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The steroids used and the groups studied were as follows:

1. Controls. Rats were injected parenterally with saline instead of a steroid. This was done daily and wounds made, sutured, and tested as in the other groups.

2. DCA (desoxycorticosterone acetate) was injected into the second group. The amount given was 5 mg. per rat each day.

3. Cortisone, 5 mg. per rat per day, was given to the third group.

4. Estradiol dipropionate, 0.25 mg. per rat per day, was given to the fourth group.

Injections of these steroids and saline were started seven days before test incisions were made and continued until the termination of each test. The choice of these drugs and groups will be discussed later.

Anesthesia.—Sodium Amytal was given intraperitoneally prior to making skin incisions. At the termination of each experiment the rats were given ether for induction followed by intraperitoneal Sodium Amytal in order to avoid any strain on the wound.

Wounds.—After carefully removing the hair with scissors, incisions with a sharp blade were made through skin and subcutaneous fat. One incision was made over each side of the chest and abdomen paralleling the midline. Each of the four incisions was approximately one inch long. The wounds were closed carefully with a fine silk mattress suture on edge at each end and a single simple suture in the center. Tests were continued for periods of 2, 4, 5, 6 and 7 days. At the end of this time sutures were removed and the wounds were tested for strength.

Wound Strength.—This was determined by a simple tensiometer. Holding sutures were placed at measured points in the skin one-half centimeter on either side of the wound margins. These sutures were then anchored to the fixed and moving elements of the tensiometer. The moving element consisted of a thread passing over a jewel-bearing pulley and attached to a test tube. Into this, droplets of mercury were allowed to pass through a fine plastic tubing. The tension of the wound was thus increased slowly until the end point was reached. The end point was established at the first break in epithelial continuity. The weight in grams which caused this break was then measured.

The manner used in placing the wounds allowed four tension tests to be determined in each rat. A histologic study could be substituted for one of the tension tests. Wounds which were infected, covered with a crust, or thought to be strained by removal of the sutures were not used.

Histologic Study.—Random wounds were excised for microscopic study at varying periods of time from two to seven days. These were stained only with hematoxylin eosin. They were studied to determine the fibroplasia and other evidence of wound healing which had taken place.

RESULTS

The large number of tests run in this investigation does not justify a detailed tabulation of every test made. We have summarized the more important

data and in part a further condensation is shown in Fig. 1. Here each of the four curves represents more than seventy wound tension tests.

As previously indicated cortisone was used in this investigation to test its ability to diminish fibroplasia and interrupt the normal progress of wound healing. The other two drugs on the other hand (DCA and estradiol) were incorporated in the study because of their reported ability to stimulate fibroplasia.[5] It was hoped that this stimulation might also improve wound healing and shorten the latent period.

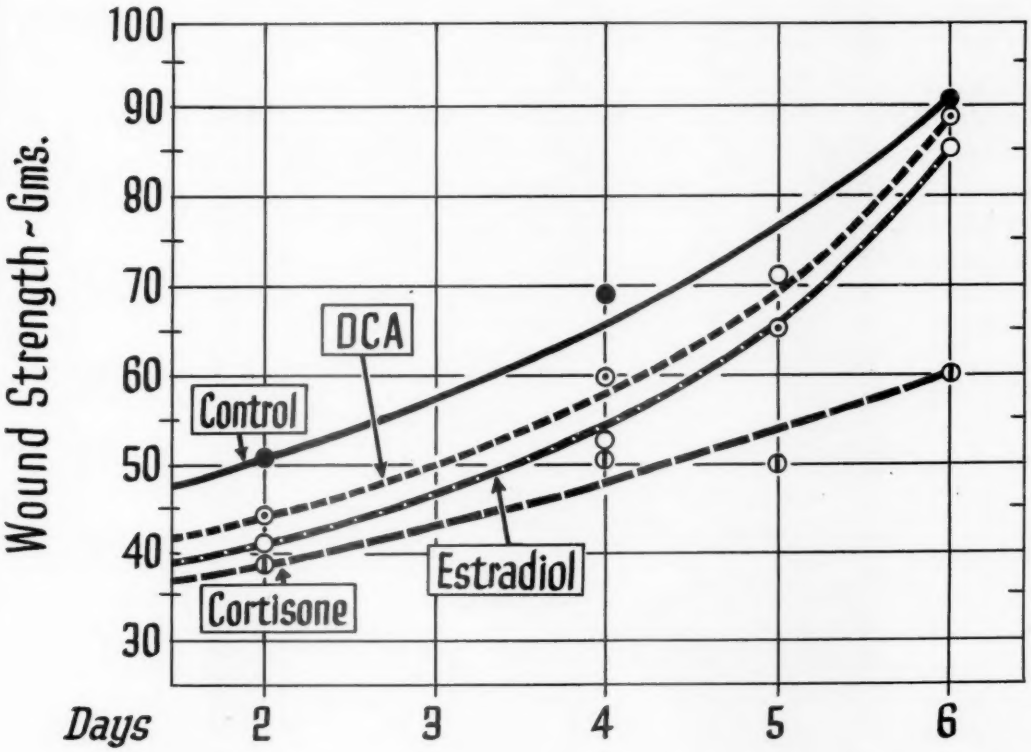

Fig. 1.—Wound healing curves indicating strength in grams of each group plotted against days healing time. Each condensed curve represents in excess of seventy wound avulsion tests.

First glance at the plotted curves of wound healing in Fig. 1 shows what might be expected in almost any wound healing study. For the control group there is a steady and regular increase in strength of the wound with the passage of time.

Figures for the third and seventh days have been omitted for clarity although they follow much the same curve. It will be noted that the groups of rats in which DCA and estradiol were used follow the same pattern as the control animals. The bottom curve indicating wound strength in the group injected with cortisone shows the expected weakening effect of this drug.

On the surface this would seem to be acceptable proof that DCA and estradiol effect no change in wound healing and strength, whereas cortisone has a definitely retarding action. Undoubtedly, some of the past reports have

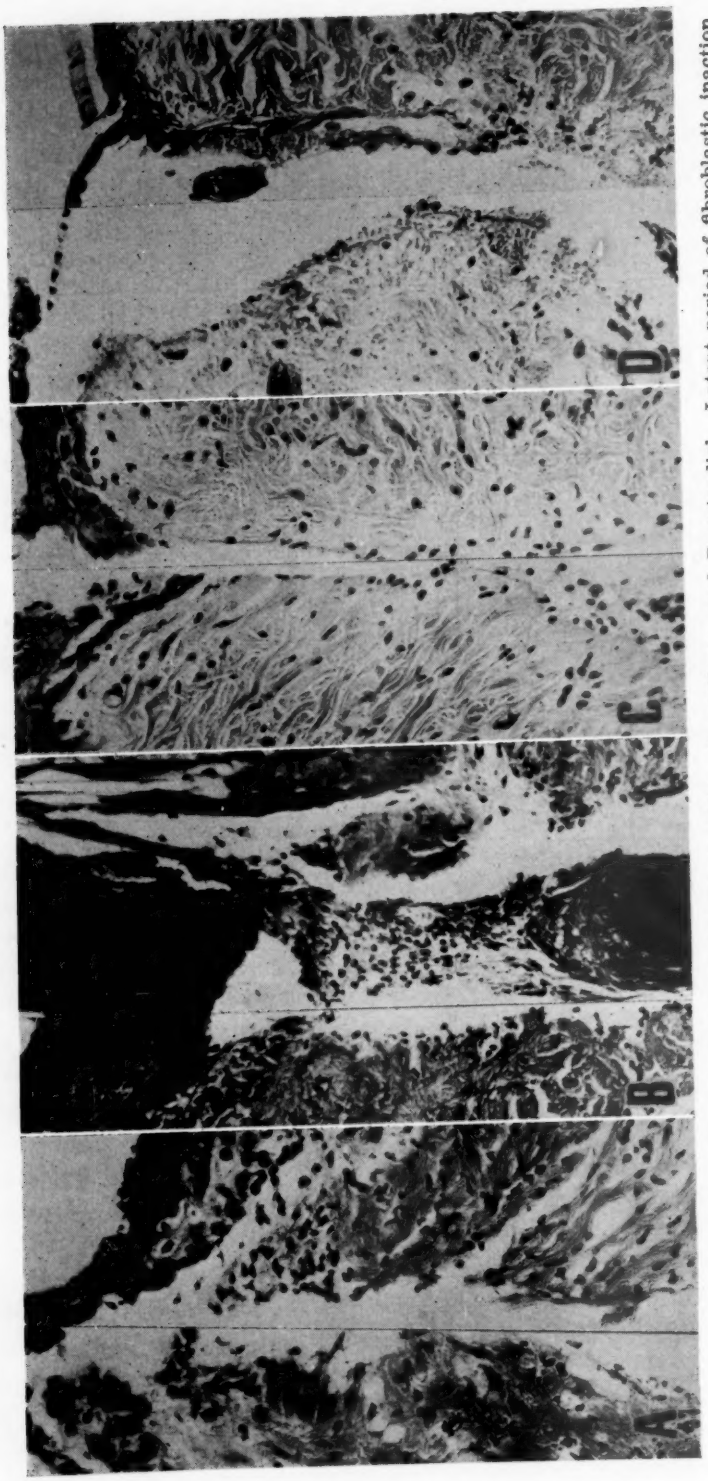

Fig. 2.—No wound healing at two days in *A*, control; *B*, DCA; *C*, cortisone, and *D*, estradiol. Latent period of fibroblastic inaction remains unchanged. Artifacts in all sections.

been built on less evidence than this. However, behind the scenes are enough flaws to cast doubt on the validity of these results.

First of all, while the plotted curves are quite regular they are made up of values far above and far below the indicated breaking points. For example the six-day wound strength of the cortisone wounds is plotted as 59.3 Gm. This value represents the average breaking strength of twenty-four separate wounds. The weakest of these broke at 40 Gm. and the strongest at 75 Gm. Even though the average produces a uniform wound healing curve this wide variation casts considerable doubt on these results (and those of others). Both the cortisone and DCA curves are statistically significant.[13] The estradiol curve was not.

Another feature which enters the picture is the fact that practically all the rats given cortisone and all the rats given estradiol lost weight during their treatment. On the other hand, all the rats in the other two groups gained weight. The controls and rats given DCA gained in average of 10 to 13 per cent, respectively, during the tests. The rats given cortisone lost an average of 7 per cent and the group receiving estradiol lost 11 per cent. Animals in these latter groups appeared ill. Possibly the doses were excessive but at least from previous reports[1, 5] the amount used was necessary to produce a therapeutic effect in the rat.

We are not alone in noting a weight loss in animals treated with cortisone. Rabbits under brief treatment in wound studies by Howes, Plotz, Blunt, and Ragan[2] had an average weight loss of 158 Gm. (6 per cent). Weight losses up to 29 per cent have been noted by others.[7] Is it not strange that this weight loss necessarily accompanies the inhibiting effect on wound healing? Can a toxic action sufficient to cause weight loss be considered as a specific depressant of fibroplasia? Does it not seem more logical to assume that an occasional wound fails to heal properly because of systemic damage which has been produced by a toxic drug and that this depressant action is by no means specific?

Histologic Study.—Representative sections of each of the four groups are reproduced in Figs. 2 and 3. Fig. 2 indicates skin wounds at 2 days and Fig. 3 at 4 days. There was no wound healing as evidenced by fibroblastic proliferation in any of the two-day sections. This was taken as evidence of failure of any of these drugs to alter the latent period, at least up to the two-day period. On the other hand all groups (including cortisone) demonstrate fibroblastic proliferation in four-day sections. True there was often less fibroplasia in the cortisone and estradiol groups (Fig. 3) but there was much overlapping in all sections of a given age and no clear-cut group demarcation. Some of the sections which show the most pronounced fibroblastic response were seen in infected wounds of the cortisone group.

DISCUSSION

In the present study we have been unable to demonstate a constant retardation of fibroplasia by the parenteral injection of cortisone. Alteration in this property of wound healing might well be the result of a systemic toxic effect rather than a specific fibroblastic depressant action. Since completing

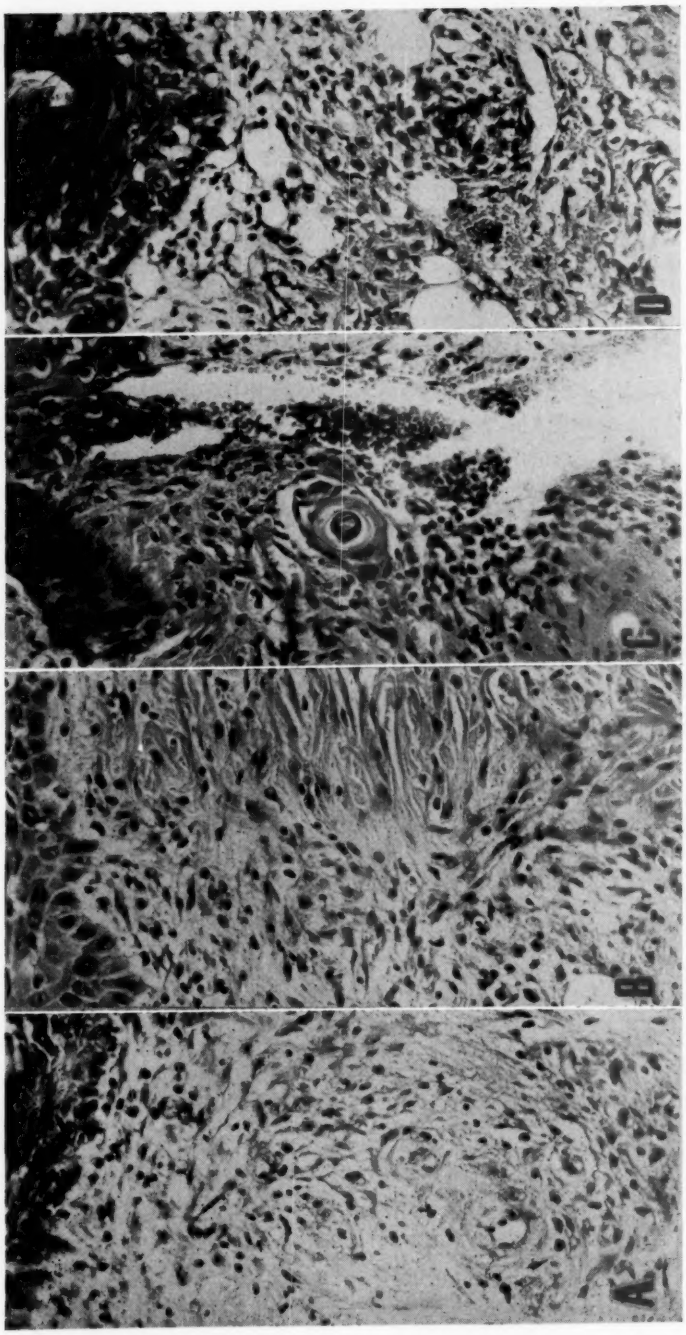

Fig. 3.—Fibroblastic proliferation of wound margins in all groups at four days. (*A*, control; *B*, DCA; *C*, cortisone; and *D*, estradiol.) In above sections *C* and *D* appear to show somewhat less fibroblastic activity. This is quite variable with too much overlapping to indicate a clear-cut tendency.

this study, others[14] have indicated an inability to reproduce completely the specific effects originally cited. Cortisone has failed to alter the growth of mesodermal tissue in vitro.[15]

There may be a specific cortisone effect delaying wound healing in some animals and under certain conditions. At present these conditions are not clear. Wounds of patients under ACTH or cortisone therapy seem to heal without incident.[14, 16-18]

The difficulty of adequately controlling wound healing studies must again be emphasized. There are so many variables in any healing wound that the addition of a specific point for study may be completely lost, or overshadowed, by those Nature has already provided.

SUMMARY

1. We were unable to demonstrate significant faulty wound healing or decreased fibroblastic proliferation following the administration of cortisone to the rat.

2. No change in the rate of wound healing was noted after the administration of DCA or estradiol.

3. None of the drugs caused an alteration in the usual or lag period of wound healing.

4. The retardation of fibroplasia ascribed to cortisone might best be explained on the basis of a profound toxic systemic effect rather than to a specific fibroblastic depressant action.

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USE OF THE ANTICOAGULANT PARITOL C IN SURGICAL CASES

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THE problem of minimizing the incidence of thromboembolic complications in postoperative patients is still one of major significance in all surgical clinics. In this respect the use of anticoagulants in recent years has received much attention, and many believe that such therapy offers the best approach to the problem that has thus far been developed. Ideal anticoagulant therapy, combining prolonged reliable effectiveness, freedom from toxic side actions, simplicity of control, and reasonable inexpensiveness, continues to tax the efforts of numerous investigators. We have recently been interested in investigating the clinical usefulness and safety of the synthetic anticoagulant agent, Paritol C,* in patients following major surgery. This drug is a highly potent preparation which resembles heparin quite closely in structure. Presumably its mechanism of action is similar to that of heparin, acting as an antiprothrombin in inhibiting the conversion of prothrombin to thrombin.[1, 2]

Reports concerning the clinical use of Paritol C by Wright and associates indicate that the drug can be used safely for effective anticoagulant therapy, in a wide variety of conditions.[2-5] We have been primarily interested in its use in those patients subjected to extensive operative procedures commonly associated with a high incidence of thromboembolic complications. Particular attention has been directed toward its safety in respect to the danger of hemorrhage from extensive raw surface areas. Accordingly, its postoperative prophylactic use has been studied in only major cases such as gastrectomies, anterior and abdominoperineal resections of the sigmoid and rectum, cholecystectomies, laminectomies, and thigh amputations.

METHOD OF STUDY

In this study, Paritol C was administered only by the intravenous route, though recently a new preparation has been developed which may prove satisfactory for intramuscular use. Dosages recommended by other investigators have varied from 3 to 5 mg. per kilogram of body weight. In our hands the lower dosage schedule proved quite adequate, and in some instances it was possible to reduce this even further. The drug was supplied to us in ampules containing 10 c.c. of a 10 per cent solution. This solution was administered slowly into the vein using a small caliber needle.

Before starting Paritol C, certain important laboratory studies were obtained in order first to detect insofar as possible any pre-existing abnormalities of the blood-clotting mechanism, and second to evaluate the kidney function, since impaired renal function has been reported to be a contraindication to its use. These studies include a complete blood count, platelet count, Lee-White

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*Paritol C (sodium polyanhydromannuronic acid sulphate) supplied for investigational use by Wyeth, Incorporated, Philadelphia, Pa.

clotting time,* prothrombin time, urinalysis, and blood urea nitrogen. In many cases several liver function tests were also obtained before and during a course of the drug.

The anticoagulant effect of Paritol C was in all instances followed by Lee-White clotting time determinations. In those cases receiving repeated consecutive doses a clotting time was obtained 8 hours after the initial injection. If this value had fallen below 20 minutes, a second injection was given. If the clotting time was 20 minutes or longer, no drug was given; and another clotting time was obtained 4 hours later. Only when the clotting time was less than 20 minutes was more drug given. Control clotting times in this series varied between 5 and 20 minutes with an average of 11.2 minutes. Within 1 to 3 days after initiation of a course of the drug, injections at 12 hour intervals proved satisfactory. Prior to that time, 8 hour intervals were necessary if a continuous effect on the clotting mechanism was to be maintained.

The 50 cases studied in this series may be conveniently divided into two groups. In the first group of 25, the effects of single and repeated injections were followed, and comparison studies with heparin were made. Also, in this group, 7 cases received single daily injections of Paritol C for from 3 to 8 days following surgery. In the second group, also of 25 cases, repeated consecutive injections of the drug were given during the postoperative period of major surgical procedures. In this group Paritol C was administered for from 3 to 7 days, with the average duration being 5.4 days.

It is in the latter phase of the study that our chief interest lies, since we are primarily concerned with the safety of the drug in patients who have been subjected to extensive surgical procedures. It is of course apparent that no conclusion as to the efficacy of this preparation in the prevention of thromboembolic complications can be made on the basis of so few cases. In most instances Paritol C was started on the second postoperative day and continued for 7 days or until the patient was discharged. The total number of injections per patient varied between 5 and 15 with an average of 9.7. The total dose of Paritol C ranged from 900 to 2,950 mg. with an average per patient of 1,671 mg. Included in this group are 4 cases of gastrectomy, 6 of cholecystectomy, 2 each of colostomy, lumbar sympathectomy, and mid-thigh amputation, one of a radical neck dissection, and one of an anterior resection of the sigmoid.

EFFECTS IN MAN

Intravenous injection of Paritol C in human beings was found to produce an anticoagulant effect lasting for periods varying from 6 to 16 hours. The clotting time following injection rapidly rose to a maximum value in about 1 hour or less and then gradually fell toward the normal range. In general the maximum effect and duration of action of a given dose could be predicted within reasonably close limits, as in the case of heparin. Thus far we have noted one instance of an effect much less and one of an effect considerably greater than that usually obtained.

*The two-tube method with dry, 10 by 75 mm. Pyrex test tubes was used for the clotting time determinations.

The first injection of Paritol C appeared to exert a potentiating effect on subsequent injections; that is, the maximum rise in the clotting times noted following the second and third injections was greater than that produced by

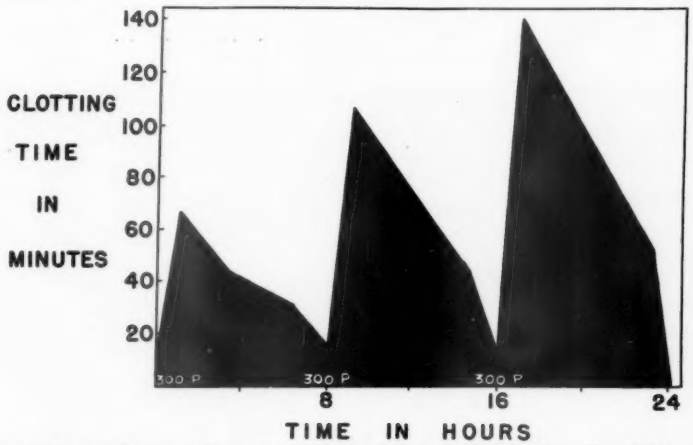

Fig. 1.—Anticoagulant effect with repeated injections of Paritol C. Note the potentiating actions of the first injection on the second and third injections.

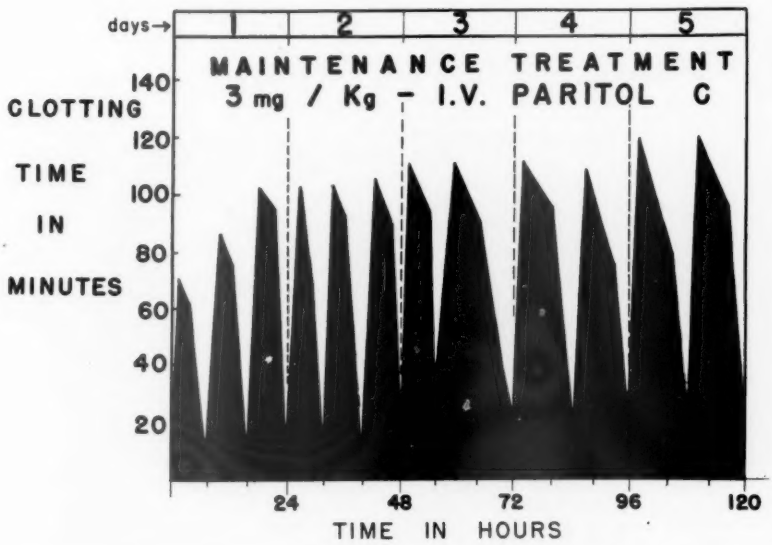

Fig. 2.—The duration of action increased from 8 to 12 hours during a three-day period in this instance.

the first (Fig. 1). Furthermore, with repeated injections the duration of action increased. In most instances the initial dose caused an effective prolongation of the clotting time lasting from 6 to 8 hours. The duration of action of a single dose was usually prolonged to 12 or even 16 hours after 1 to 3 days of consecutive repeated injections (Fig. 2). From these data it may be seen that the action of an initial dose cannot be used as a guide to prolonged therapy, and furthermore that repeated checks on the Lee-White clotting times are necessary during a course of the drug to properly control its effect.

COMPARISON WITH HEPARIN

In our experience Paritol C is approximately one-third as potent as heparin; i.e., three times the amount of Paritol C by weight must be administered intravenously to obtain comparable elevations of the clotting time in the same patient. With heparin the clotting time invariably returned to normal within a 4

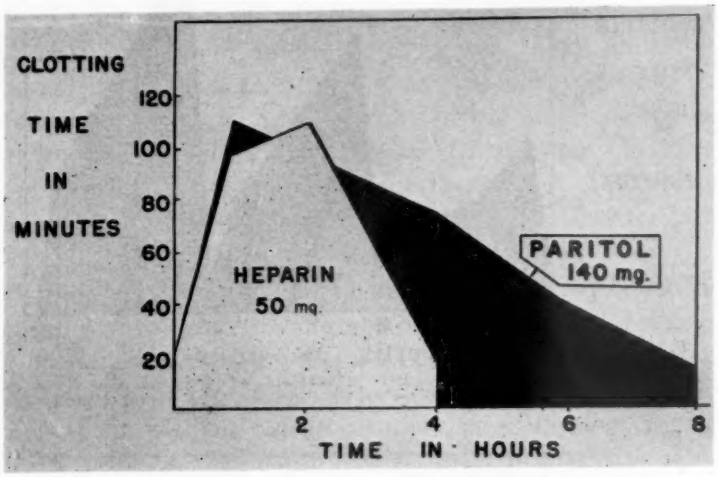

Fig. 3.—Comparison of anticoagulant effect of Paritol C and heparin. The longer duration of action of Paritol C as compared to heparin is apparent.

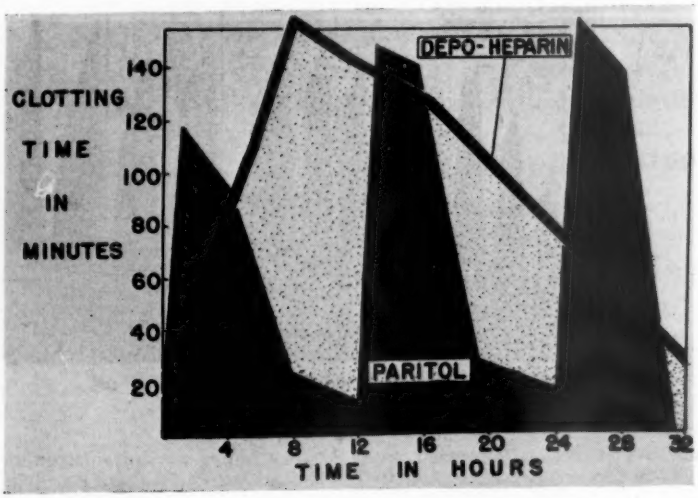

Fig. 4.—Comparison of the anticoagulant effect of Paritol C and repository heparin. Three injections of Paritol C necessary to sustain an anticoagulant effect comparable to 200 mg. of heparin in respository form.

hour period, while with Paritol C the clotting time remained significantly elevated for 6 to 8 hours (Fig. 3). When heparin was given intramuscularly, essentially the same relationships obtained, except that the maximum rise of the clotting time produced by heparin in this form was much lower. A comparison was also made between a usual dose of heparin in a repository form (200 mg.) and repeated injections of Paritol C. Heparin in this form main-

tained effective prolongation of the clotting time for 32 hours, while 3 injections of Paritol C were necessary to achieve a similar effect (Fig. 4). With continuous, prolonged use of Paritol C, prothrombin time values obtained daily showed a moderate decrease over a period of several days in most cases.

RESULTS IN POSTOPERATIVE SERIES

As noted previously there were 25 patients who received repeated consecutive injections of Paritol C in the postoperative period of major surgery. A sustained, adequate anticoagulant effect as illustrated in Fig. 2 was maintained in 23 of the 25 cases without evidence of any toxic manifestations or other untoward complications. In 2 of the cases complications developed during or immediately following discontinuance of the drug, and these will be discussed in detail in a following section.

In 5 instances the drug was discontinued short of the desired time. In 1 of these the injections were stopped because of a complication. The superficial veins in 1 patient were poor and urgently needed for parenteral feedings, and 2 patients objected strenuously to the numerous venepunctures. Finally, in 1 case the drug failed to produce the usual effect on the clotting time except to a small degree, the maximal prolongation being to 26 minutes, and hence was discontinued after 5 injections. Manchester mentions a similar case in his series.[6]

COMPLICATIONS

Bleeding.—In this series of 50 cases, 2 instances of bleeding occurred during the period of injection. The first was in a 41-year-old man who received Paritol C injections for 3 days during the postoperative period of a bilateral lumbar sympathectomy. On the third day of the drug a small, subcutaneous wound hematoma developed, at which time therapy was discontinued. The wound healed promptly after evacuation of the hematoma, and the further course of the patient was uncomplicated. In the second such case the role of the anticoagulant therapy is uncertain due to other serious complicating factors. This patient, a 58-year-old white woman, entered the hospital in very poor condition, appearing acutely and chronically ill, and with massive thrombophlebitis of the left leg and gangrene of the left foot. Three injections of Paritol C were given with the usual response and with return of the clotting time to normal before each subsequent injection. Following the third injection the patient passed a tarry stool, became very restless during the ensuing 8 hours, and died, complaining terminally of severe chest pain. At autopsy significant findings were multiple pulmonary emboli and infarctions, thrombophlebitis of the left leg, gastrointestinal hemorrhage, and carcinoma of the gall bladder with invasion of the omentum and metastases to the liver. The gastrointestinal tract contained a considerable amount of digested blood, but how much of a part this played in causing the patient's death, and whether the anticoagulant therapy was the factor responsible for the bleeding are doubtful points.

Thromboembolism.—Two patients in this series developed thromboembolic complications during the period of observation. In one patient, 5 injections

of the drug were given following reduction of a small bowel volvulus. However, as noted above, in this case the drug produced relatively small elevations in the clotting times and hence was discontinued. This patient, who in addition had auricular fibrillation, developed an embolic occlusion of the left popliteal artery the day following discontinuance of Paritol C. Following this incident his condition rapidly deteriorated, and he died 2 days following the occlusion.

The second such instance was one of that group who received single daily injections over a period of several days. This patient received 8 daily injections of Paritol C beginning on the second postoperative day following abdominoperineal resection for carcinoma of the rectum. The day after the drug was stopped a small pulmonary infarction was suspected clinically and confirmed by chest x-ray. The patient recovered promptly and without further sequelae from this incident. No signs of venous thrombosis in the leg veins were detected at any time. It should be pointed out that in this case no attempt had been made during the course of drug administration to maintain a continuous anticoagulant effect.

DRUG REACTIONS

The toxic manifestations of this drug in these cases were few and of minor significance. In 1 case a single injection of the drug apparently produced a sensitivity reaction manifested by swelling, stiffness, and discomfort of the wrist and finger joints and by a burning sensation in the soles of the feet. These symptoms began about 1 hour after the injection and subsided spontaneously in 8 hours with no treatment. Two other patients, who also received single injections, complained too of this burning sensation in the soles of the feet. It may be of significance that all of these reactions occurred early in the study, and none have been noted with later lots of the drug. As far as could be determined on the basis of repeated liver function tests and complete blood counts, the drug had no effect on the liver or hematopoietic system.

CONCLUSIONS AND SUMMARY

1. Use of the synthetic anticoagulant, Paritol C, in 50 cases is reported, with particular emphasis being placed on its use in postoperative patients.

2. The drug raises the clotting time to effective levels for periods varying from 8 to 16 hours. The initial injection potentiates the action of subsequent injections as measured by the maximum clotting times obtained. After 1 to 3 days of continuous therapy the duration of effective action is prolonged from about 8 to 12 hours.

3. It has two principal drawbacks: first, it must be given intravenously, thus imposing a burden on the professional staff; and second, frequent determinations of the clotting time have been considered necessary for its control. The first mentioned disadvantage may soon be overcome with recently prepared preparations for intramuscular use. The necessity for rather frequent venepunctures causes a certain amount of discomfort for the patients.

4. As in the case of all anticoagulants, the drug carries the hazard of bleeding complications. We have seen one such major incident, gastrointestinal hemorrhage, possibly related to the anticoagulant, and one minor complication, a small wound hematoma. The incidence of toxic manifestations thus far observed has been small, and these have been of minor significance.

5. The drug when marketed will probably be relatively inexpensive as compared to heparin.

6. We believe the drug merits extended clinical trial to further evaluate its properties and to make possible significant statistical studies on its effectiveness in the prophylaxis of thromboembolic disease.

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CARCINOID OF THE STOMACH

Review of Reported Cases

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THE original description of carcinoid tumors was made by Langhans,[1] in 1867, although they were not recognized as such. A small polypoid tumor was reported involving the submucosa and muscularis layers of the ileum and presenting an infiltrating alveolar structure. In 1888, two cases of atypical primary carcinoma of the small intestine were described by Lubarsch[2]; who felt that they arose from the crypt cells. In 1890, Ransom[3] reported the first malignant argentaffinoma originating in the ileum and metastasizing to the liver. This was the original attempt at distinguishing this type of cell from the cylindrical-cell adenocarcinoma occurring in the gastrointestinal tract. Silver impregnation staining method was utilized and showed a definite relationship between the tumor cells and the crypts of Leiberkühn.

Oberndorfer,[4] in 1907, designated these tumors carcinoid and demonstrated the chromaffin bodies in their cytoplasm. He believed that they were embryonal malformations. Huebschmann,[5] in 1910, suggested that they might arise from chromaffin cells. Gossett and Masson,[6] in 1914, showed the affinity of certain granules in the cytoplasm of the cells for silver salts. These were designated argentaffin cells and hence the lesions were called argentaffinoma. Much has been written about carcinoid, especially of the appendix and small intestine, but only seventeen cases of carcinoid of the stomach have been reported. The first two cases were reported by Askanazy,[7] in 1923. In 1939, Plaut,[8] reported nine cases of carcinoid of the stomach; thus, the infrequency of this lesion is obvious. Table I summarizes the cases reported, in addition to the one which is presented.

CASE REPORT

A 46-year-old white woman was admitted to Emory University Hospital on July 28, 1950, with the chief complaint of menorrhagia. The abnormal bleeding had been present for about six months. For the past three years, she had been treated by her physician for pernicious anemia. There had been, for the past year, occasional attacks of nausea and vomiting. This had been associated with some weakness but no weight loss.

Physical examination revealed a moderately obese woman, who was otherwise normal except for the uterus. The uterus was enlarged, irregular, nodular, and about the size of a grape fruit. It was freely movable and consisted of what was thought to be multiple fibroids.

Laboratory examinations were essentially negative. Gastrointestinal roentgenograms revealed a small filling defect, which had the appearance of a polyp of the stomach in its lower anterior mid-portion. The esophagus and duodenum were normal. The finding of this lesion in the stomach, which was thought to be a polyp, was considered the major problem at that time.

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TABLE I. SUMMARY OF THE EIGHTEEN REPORTED CASES OF CARCINOID OF THE STOMACH

YEAR REPORTED	AUTHOR	LOCATION	SIZE	METASTASIS	AGE	SEX	SYMPTOMS	RESULT
1923	Askanazy[7]	2 mm. above pylorus	3 × 4 × 3 mm.		80	F	Incidental finding	Died—bronchopneumonia
1923	Askanazy[7]	Lesser curvature	11 × 7 × 2 mm.		89	M	Incidental finding	Died—bronchopneumonia
1928	Masson and Martin[9]	Prepyloric region		Yes	41	M	Those of gastric ulcer	No follow-up
1930	Paltauf[10]	Stomach	Lentil		64	F	Incidental finding	Died—kidney disease
1933	Raiford[11]	Greater curvature		Yes, liver and lymph nodes	55	M	Indigestion—10 mos. weight loss 15 lbs.	Inoperable—died in few days
1934	Feyrter[12]	Fundus	Larger than lentil		66	F	Unknown	Died
1934	Feyrter[12]	Fundus	Pea sized		56	M	Unknown	Died
1934	Bailey[13]	Lesser curvature. 4 cm. below cardia	13 mm.		66	F	Incidental finding	Died—erysipelas
1935	Pettinari[14]	Pyloric region	3 cm.	No	47	M	Pyloric obstruction	Discharged well
1936	Entwisle[15]	5 tumors	Largest 3 cm.		25	F	Mod. abd. pain, nausea, hematemesis	Gastrostomy recovery
1937	Walley[16]	Greater curv. post. wall	1 × 1.5 cm.	No	41	M	Epigastric pain for years	Excision—did not affect symptoms
1939	Plaut[8]	Lesser curvature	1.5 × 3 cm.		69	F	Incidental finding	Died
1939	Porter and Whelan[17]	Stomach		No	60	F	Incidental finding	Died—bronchopneumonia
1939	Porter and Whelan[17]	Stomach		No	40	M	Incidental finding	Died—endocarditis lobar pneu.
1942	Lemmers[18]	Cardia 2 tumors	7 × 6 × 5 and 1 cm.		44	F	Bloody stools, upper abd. pain	Gastric resection, recovery
1947	Ehrlich and Hunter[19]	Stomach	1 cm.	No	?	?	Unknown	Apparent recovery
1949	Jonsson[20]	2 cm. below cardia	3 cm.		68	F	Epigastric pain, dark stools and hematemesis	No symptoms
1951	Martin and Atkins	3 cm. above greater curvature	1 cm.	No	46	F	Nausea and vomiting	Asymptomatic at the end of one year

After adequate preparation, on Aug. 19, 1950, under general anesthesia, the abdomen was opened. When the stomach was examined, there was noted a well-circumscribed, reddish brown, raised mass on the anterior wall about 3 cm. above the greater curvature. It measured 2 cm. in diameter and was raised ½ cm. above the serosal surface. The lesion was not ulcerated and was located between the serosa and mucosa. A resection of the mass was made, including a wide area of normal stomach.

The specimen consisted of an elliptically excised portion of stomach wall, which contained on its serosal surface a 1 cm. nodule which protruded from the capsule. The cut surface was pinkish gray in color and soft in consistency.

On microscopic examination, a mass of small round cells with a granular eosinophilic cytoplasm and round dark-staining nuclei, arranged in cords, was seen. Lymph canaliculi were seen throughout the tumor. The borders showed slight invasion of the muscle bundles, but, for the most part, the tumor seemed to be displacing the muscle fibers.

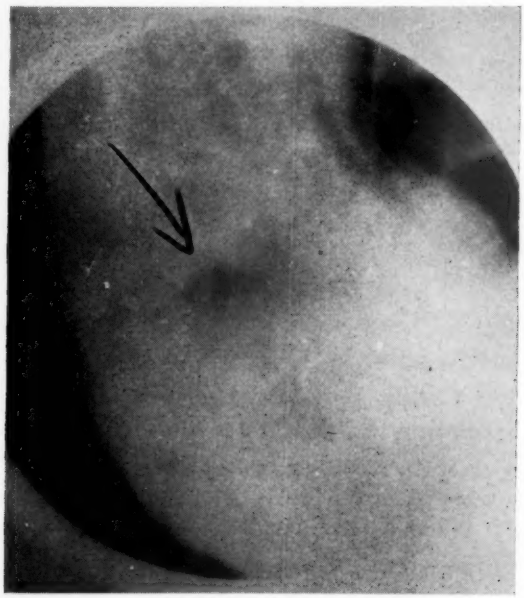

Fig. 1.—Roentgenogram of stomach showing defect in its central portion.

Convalescence was uneventful, following operation, until February, 1951, when it was noticed that the skin was deeply jaundiced. The patient was readmitted to Emory University Hospital on Feb. 22, 1951.* She presented a clinical picture compatible with Homologous Serum jaundice, presumably caused by the blood transfusions received on her previous hospital admission. Physical findings, laboratory tests, and course substantiated this diagnosis. She had an uneventful recovery and was discharged from the hospital on March 11, 1951. The jaundice has since completely disappeared. During this hospital admission, a gastrointestinal series was done, with normal findings. At the present time, the patient is free of symptoms.

Masson[21] has shown that carcinoid tumors contain cytoplasmic granules, which reduce silver ammonium oxide. It has also been demonstrated that these granules are present in the Kultschitzky cells, in the crypts of Lieberkühn. They occur occasionally in the stomach, are moderately abundant in the jejunum and ileum, numerous in the duodenum, most frequent in the appendix, and can be demonstrated in small numbers in the colon. The incidence of carcinoid

*She was seen by Dr. Charles Hughley.

tumor in different locations roughly parallels the frequency with which the Kultschitzky cells are found.[22] Gaspar[23] showed by serial sections that the carcinoid tumor arises from the cells of the crypts of Lieberkühn.

The carcinoid tumor usually appears as a single nodule between the mucosa and muscular layers of the gastrointestinal tract. It is small, firm, rubbery in consistency. On cut section the color is usually grayish yellow. It may extend into the muscularis layers and may ulcerate into the mucosa with subsequent hemorrhage. The more malignant tumors are usually larger and are often multiple. The regional lymph nodes are first invaded and later metastases occur in the liver. The cells of both the primary tumor and metastases contain silver-reducing granules in the basal portions.

The cells are strikingly uniform and arise from the normal epithelium growing into the submucosa. They have an eosinophilic cytoplasm and a centrally placed spherical nucleus. Mitoses are very infrequent. The nests of cells are separated with a dense stroma and are encapsulated by smooth muscle and connective tissue. The capsule is a false one and offers little resistance to the invasion of the tumor cells. The characteristics of the cellular morphology do not indicate the malignancy, but this is shown by the clinical course. With these invasive properties, the metastases occur very slowly, regardless of the location of the tumor.

Most tumors found in the appendix are carcinoids. It has been shown that these lesions are found in 0.2 per cent of all removed appendices. Signs and symptoms are suggestive of appendicitis, and thus the appendix is removed, which accounts for the large number of verified diagnoses. Carcinoid is twice as frequent in the appendix as in the small intestine, which is the next most usual location.[24] Ashworth[26] reported twenty-eight cases of carcinoid tumor in locations other than the appendix and small intestines. The following is the order of frequency: colon—11, diverticulum—7, stomach—6, gall bladder—2, mesentery—2.

Lesions of the small intestine frequently present symptoms of obstruction. In 152 cases reported by Humphries,[24] intestinal obstruction occurred in 24 per cent. Most obstructions are apparently due to the angulation from the mesenteric metastasis, rather than to the actual tumor itself.

The rectum is the next most common location. A total of forty-eight cases of rectal involvement have been reported by Shepard.[25] Ten of thirty-two were symptomatic, with melena and pain as the most frequent accompaniment.

Eighteen reported cases of carcinoid of the stomach have been found, which verifies the rarity of this lesion. It is felt that in this location symptoms are rarely experienced and many may be overlooked.

Carcinoids are not peculiar to any age, but the average age varies with the location. Raiford[11] reports that tumors of the appendix occur at an average age of twenty-five years, the small intestine, fifty-five years, and the colon, forty-five years. In those of the stomach, the ages ranged from twenty-five to eighty-nine years, with the average being fifty-six.

Definite symptoms were encountered in eight of these eighteen cases. This is a much higher number having symptoms than has been reported previously.[11]

Carcinoid of the stomach can produce symptoms similar to any lesion of the stomach. It is more often symptomatic in this location than in the rectum.

The differentiation between malignant and benign tumors cannot always be made histologically, but rests on the clinical course. These tumors appear

Fig. 2.

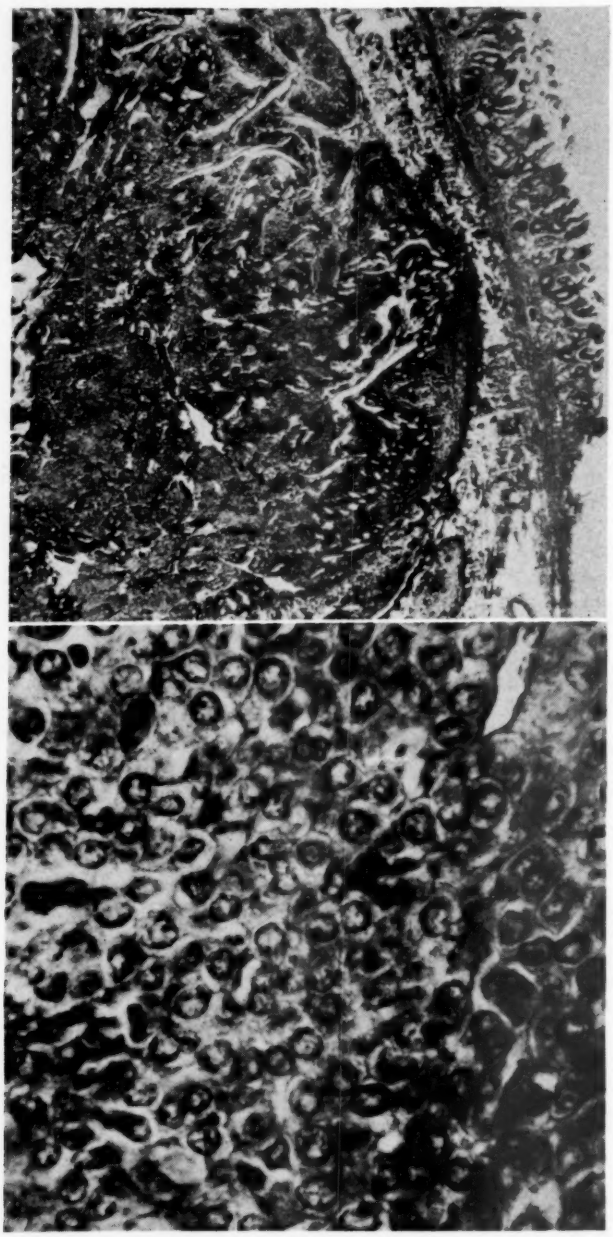

Fig. 3.

Fig. 2.—Low-power photomicrograph demonstrating the nests of tumor cells located beneath the submucosa and muscularis layers of the stomach wall.

Fig. 3.—High-power magnification of the characteristic cells demonstrating a distinct cell wall with granular cytoplasmic substance.

benign but may have properties of malignancy. They grow slowly and metastasize late; therefore, must be considered malignant. The manner of invasion is by lymphatic and venous systems. Regional metastases are common, but distant involvement is rare. The lesions in the appendix are seldom malignant as has been shown in the sixty-five cases reported by Ehrlich,[19] none of which metastasized. As was previously noted, the early removal may account for this.

It is generally agreed that about 22.5 per cent of carcinoids of the small intestine are malignant. Raiford[11] reported two of his nine cases as being malignant, which is an incidence of 22 per cent. Humphries[24] reported 24.4 per cent of the 152 cases reviewed as malignant. Cooke[28] reported twenty-one malignant and eighty-three benign carcinoid tumors of the small intestine. Metastases were found in 20 per cent of the 104 cases. The liver was involved in eight of the twenty-one cases, regional lymph nodes in eleven, and serosa in three. These reports are substantially in agreement regarding the incidence of malignancy.

Altman and Mann[27] note the incidence of malignant carcinoids other than the appendix and small intestine as being 25 per cent. Shephard[25] found seven of forty-eight rectal cases showed extensive invasion. No malignancies were encountered in ten cases reported by Ehrlich.[19] However, the average age was less than in those with carcinoid of the rectum. Ashworth reported twenty-five cases of carcinoids in unusual locations and, of these, 25 per cent were malignant. Eleven per cent of the group involving the stomach were malignant, all showing metastasis.

The accepted method of treating carcinoid of the stomach is adequate surgical removal. There is no agreement, however, as to the type of surgery which may be necessary. A wide excision of the lesion itself and an adequate removal of the noninvolved portion of the organ may suffice in the early benign lesions. However, total gastrectomy and the removal of regional lymph nodes may be in order. It is doubtful, however, that such treatment would result in a more favorable prognosis, since early diagnosis is almost impossible. Surgical removal of the primary lesion may be necessary to remove an obstructing mass or one that may be producing symptoms as a result of its location, after liver metastases have occurred. Many patients may be expected to live for a long period even with extensive metastases. Radiation therapy is seldom utilized since these tumors are radiation resistant.

It is obvious, from the above description of the pathologic aspects and the mode and frequency of metastasis, that the prognosis is generally good. In this group of reported cases, all deaths were attributable to other causes, except one. Since involvement of the appendix and small intestine, presents early symptoms, operative removal improves the prognosis and rarely would metastasis be expected. This is particularly true since these tumors are slow growing and metastasize late.

SUMMARY

A review of seventeen cases of carcinoid tumor of the stomach is made. An additional case is reported, which was recognized during a routine examination.

The usual pathologic manifestation is that of a benign lesion which is located in the gastrointestinal tract as a small tumor between the mucosa and the muscular layers. The most common sites being the appendix, small intestine, colon, and stomach, in that order of frequency.

The occurrence of carcinoid of the stomach is extremely rare but the course is no different from similar lesions in other parts of the gastrointestinal tract. Seldom are symptoms produced from the tumors of the stomach until they have become malignant. Malignancy rarely occurs, and when it does, metastases take place through the regional nodes.

Removal of the lesions early is accompanied by a most favorable prognosis. Wide excision may be sufficient, although total gastrectomy may be necessary.

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DERMATOFIBROSARCOMA PROTUBERANS

A Review of the Literature and Presentation of Three Cases

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DERMATOFIBROSARCOMA protuberans is a clinical-pathological entity which the general surgeon may encounter infrequently but with which it would be well for him to be acquainted since the ultimate success of the surgical management of this lesion often is determined by its initial treatment. It is the purpose of this paper to review the significant literature on the subject, to indicate the important clinical and pathological features, and to report three cases that have been seen in this hospital.

Darier and Ferrand,[4] in 1924, presented what is generally recognized today as the first complete description of this lesion under the name of "Progressive and Recurring Dermatofibromas." These authors separated these tumors from the sarcomas in general on a clinical and histological basis. They indicated that a previous description of a case had been reported by Unna in his book on histopathology in 1896.[21] This lesion had been reported in this country prior to Darier and Ferrand's description under various other names, such as "Sarcomatous Tumors Resembling in Some Respects Keloid,"[20] "Fibrosarcoma Cutis,"[9] and "Sarcoma and the Sarcoid Growths of the Skin."[10]

Hoffmann,[8] in 1925, reported 3 cases of the lesion and reviewed 12 cases that he found in the literature. According to Hoffmann, the first authentic reported case of the disease was that published by Coenen[3] in 1909. Hertzler,[7] in 1926, reported 22 personally observed cases of which only one was above the clavicle. McMaster[11] presented 39 authenticated cases including 1 of his own. Since then, numerous case reports have appeared in the domestic and foreign literature.[2, 5, 6, 12-14, 16, 19, 22] In the case reported by Niedelman[14] the lesion had developed on an old burn scar in a 48-year-old white man who had been severely burned at the age of 6 years.

Pack and Tabah[15] have recently presented a summary of their experience with 39 cases seen at the Memorial Hospital in New York City over a 20 year period. This brings the total number of cases that we have been able to find reported in the world literature to 187, not including the cases herein reported. This number obviously does not represent the true incidence of this tumor which in the experience of Pack and Tabah was slightly less than 0.1 per cent of all tumors seen over a 20 year period. The 3 cases reported in this paper represent the sum total of cases seen in a large Veterans Administration Hospital and Tumor Center since adequate records were established in the pathology laboratories in 1946.

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CLINICAL PICTURE

From the reported cases, it appears that men are more frequently affected than women,[12, 15] in a ratio of approximately 3 to 2. The tumor in the reported cases has had an unusual predilection for the anterior surface of the body to the right and left of the midline, although in Pack and Tabah's series the lesion occurred equally frequently on the chest, back, abdomen, upper thigh and groin.[15] The lesion has also been observed less frequently on the extremities, buttocks, head, scalp, and genitalia. The histogenesis of the lesion is still in dispute. Pack and Tabah[15] feel that this lesion is essentially a fibromatous or fibrosarcomatous tumor with the fibroblast as the basic cell, and differentiated clinically from other desmoplastic tumors by its location, appearance, and manner of growth. Binkley[2] suggested that the origin of these tumors was from mammary tissue because of the close proximity of the tumors in the reported cases to the mammary ridge. Trauma has been incriminated by some authors as a possible contributing factor. Two of our cases had a definite history of trauma to the tumor site preceding the appearance of the tumor. Pack and Tabah found a history of trauma in 13 per cent of their cases and concluded that it was not a significant etiological factor. There has been no evidence to support the theory that dermatofibrosarcoma arises from nerve tissue. It should be emphasized, however, that these lesions are frequently misdiagnosed histologically as neurofibromas or neurogenic sarcomas. Such was the situation in one of our own cases (Case 1).

Michaud[12] has pointed out that the evolution of the tumor is in two stages. The first stage consists of the development of a firm plaque in the skin and may be referred to as the "fibrous plaque" stage. The onset of this stage is insidious. An indurated plaque may develop within the skin, or several hard nodules may develop in the skin and then become confluent to form the plaque. This plaque grows very slowly by peripheral extension, and is poorly defined. The color of the lesion varies, although it has frequently been described as being pink, brown, or "dense blue."[18] On palpation, the plaque is very hard with a slightly lobulated surface. This plaque remains intracutaneous, is always movable over the underlying tissues, and is nontender.

The second or "tumoral" stage usually develops after the "fibrous plaque" stage has been present for many years. Single or multiple tumors covering a wide surface develop on the fibrous plaque, which, however, retains its original characteristics. A very constant feature of these tumors, from which Hoffmann[8] derived their name, is their protuberant character. The tumors may be pedunculated or sessile, are nontender, and may be white, yellow, dark red, violet, or purplish in color. In contrast to the slow growth of the fibrous plaque, these tumors grow rapidly and may reach the size of a lemon in a few months. The lesions are hard, with no tendency toward necrosis or softening, although the overlying epidermis may become eroded.

The clinical picture of dermatofibrosarcoma protuberans is that of a low-grade malignant tumor that grows very slowly and tends to recur locally. Hoffmann[8] compared this lesion with its local malignancy and its intermediate

position between fibroma and sarcoma, to basal-cell epithelioma in its position between benign epithelial growths and squamous-cell cancer. It has been stated that glandular or visceral metastases do not occur.[12, 18] However, Binkley[2] presented one case that died of "tumor metastases" although he did not state where these metastases were or whether these "metastases" had been examined histologically following necropsy. In addition, there have been reports of fatal lung metastases from dermatofibrosarcoma protuberans in the foreign literature.[1, 17]

The tumors are resistant to radiotherapy or electrolysis, and recur rapidly with increased rapidity of growth after incomplete surgical removal. The treatment of choice, therefore, is *adequate* and *complete* surgical extirpation. This surgical removal must include not only the superficial tumor nodules, but also the underlying fibrous plaque together with several centimeters of surrounding normal skin and subcutaneous tissue. Pack and Tabah[15] recommend routine removal with the specimen of the fascia overlying the muscle deep to the lesion. The tumor is almost always confined to the skin and hypodermis, although there have been reported cases in which underlying muscle was involved. In one of our cases (Case 1), the tumor had invaded the anterior rectus sheath and muscle belly requiring partial removal of the rectus muscle. The defect left after removal of the lesion may be large enough to require skin grafting. In Pack and Tabah's series, amputations for these lesions occurring on the extremities has never been necessary.

PATHOLOGIC FEATURES

On section, the fibrous plaque is found to consist of very hard, thickened corium. The epidermis is slightly atrophied and the corium is formed of myxomatous connective tissue with large lacunar spaces. The tumors themselves consist of fusiform cells in streaks with abundant protoplasm and clear nuclei. Between them are collagen fibers, and in the region of rapid growth many mitoses may be seen. The elastic tissue is conserved but is dissociated. Many vessels have a lacunar structure similar to that found in fibroblastic sarcomas. There is no capsule, and the tumor is in contact with the epidermis. As stated previously, the differentiation of this tumor from other fibrosarcomas is sometimes not made microscopically but is based upon a clinical appraisal of the history and physical examination.

CASE HISTORIES

CASE 1 (Register No. 138071).—

History.—J. A. N., a 59-year-old white married man, was admitted to the Bronx Veterans Administration Hospital for the first time on Aug. 20, 1940. The patient stated that in 1922 he first noticed a small lump in the skin just above the umbilicus. There was no history of trauma, and no local pain. In the same year, the patient went to his family physician who excised the growth under local anesthesia in his office. The wound healed completely in 2 to 3 weeks.

In 1924, the patient noticed a recurrent growth in the same area which grew to the size of a small egg. This was excised at another hospital and the wound healed completely in 2 weeks. There was no further trouble until 1938 when the patient noted a recurrent

growth in the same area. The lesion, according to the patient, "seemed to have spread out more." The growth was once more excised at another hospital and again the wound healed promptly. In December, 1939, the third recurrence developed, this time increasing in size more rapidly. The patient had been advised to have surgery performed, and presented himself at this hospital for treatment. There was no history of weight loss. There was no pain except occasional soreness in the region of the growth.

Physical Examination.—A large protruding tumor about the size of a baseball was noted on the anterior abdominal wall. It measured 9 by 11 cm. and projected about 5 cm. above the level of the abdomen. The overlying skin was tense and shiny, and the tumor was very firm and freely movable with the skin. It seemed to be free from, and above, the muscle layer.

Clinical Course.—On Sept. 6, 1940, under spinal anesthesia, the entire tumor was removed including normal skin around the lesion and the underlying muscle fascia to which the tumor was attached. The pathologist reported the lesion as a neurofibroma of the abdominal wall.

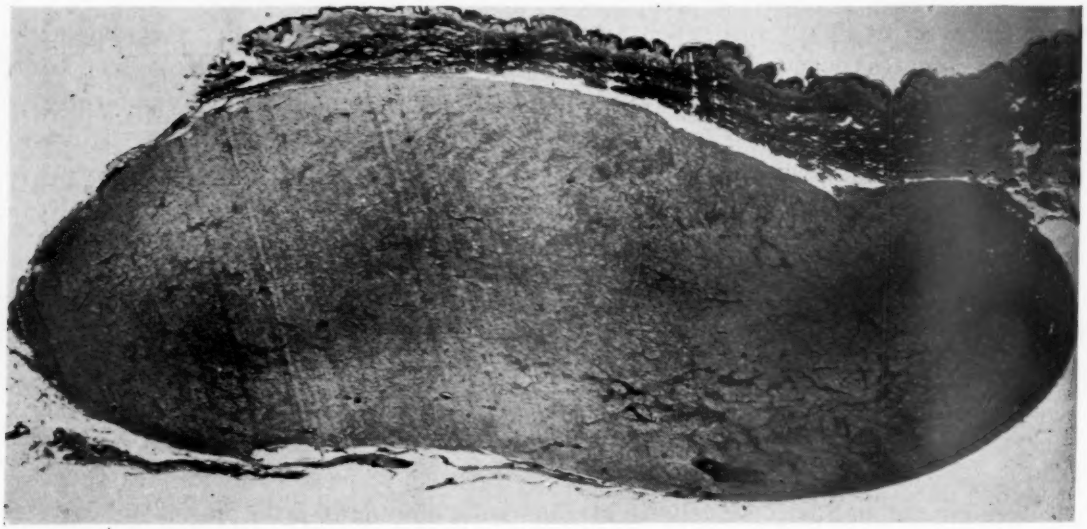

Fig. 1 (Case 1).—Low-power view of most recent recurrence excised. Note how well demarcated lesion appears grossly, and its relationship to the overlying epidermis. (×9.5.)

The patient was readmitted to the Bronx Veterans Administration Hospital on March 9, 1942, because of a recurrence which was noted several months after discharge from this hospital in 1940. System review and chest x-ray were negative. On examination, the patient had an irregular postoperative scar over the left central portion of the abdominal wall with an orange-sized mass in the scar which was soft and nontender. There was no adenopathy. On March 17, 1942, under combined spinal and general anesthesia, this recurrent tumor mass was excised with a surrounding ellipse of normal skin. This resection included approximately 4 inches of the belly of the left rectus muscle through which the tumor had penetrated. The pathologic report was cellular neurofibroma.

The patient re-entered the hospital on March 5, 1945, because of a recurrent mass at the same site which had developed during the two months prior to admission. There had been no pain or loss of weight. System review was negative. Chest x-ray was negative for metastatic disease. On physical examination, there was a transverse supraumbilical scar running from the right of the epigastrium to the left costal margin. At the right end of the incision, there was a chestnut-sized, hard, regular mass which was fixed to the skin but not to the deep structures. It was not tender on palpation. Just below the left extremity of the incision was a pea-sized subcutaneous node. The abdominal wall above the whole length of the incision was hard. On March 16, 1945, under local anesthesia, the

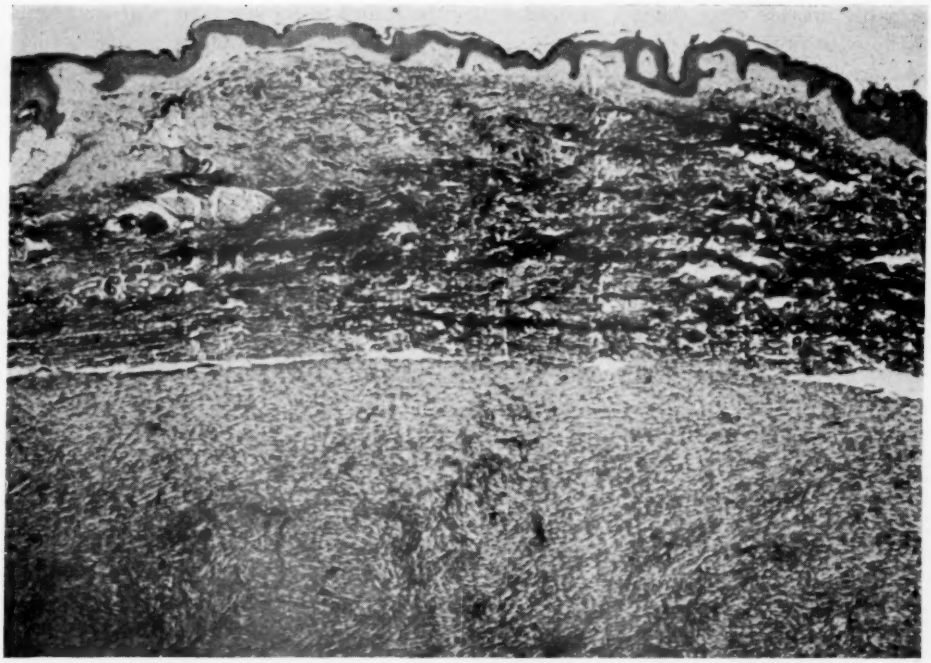

Fig. 2 (Case 1).—Higher power view of slide of Fig. 1. Note again the well-demarcated line between the corium and the tumor. (×52.)

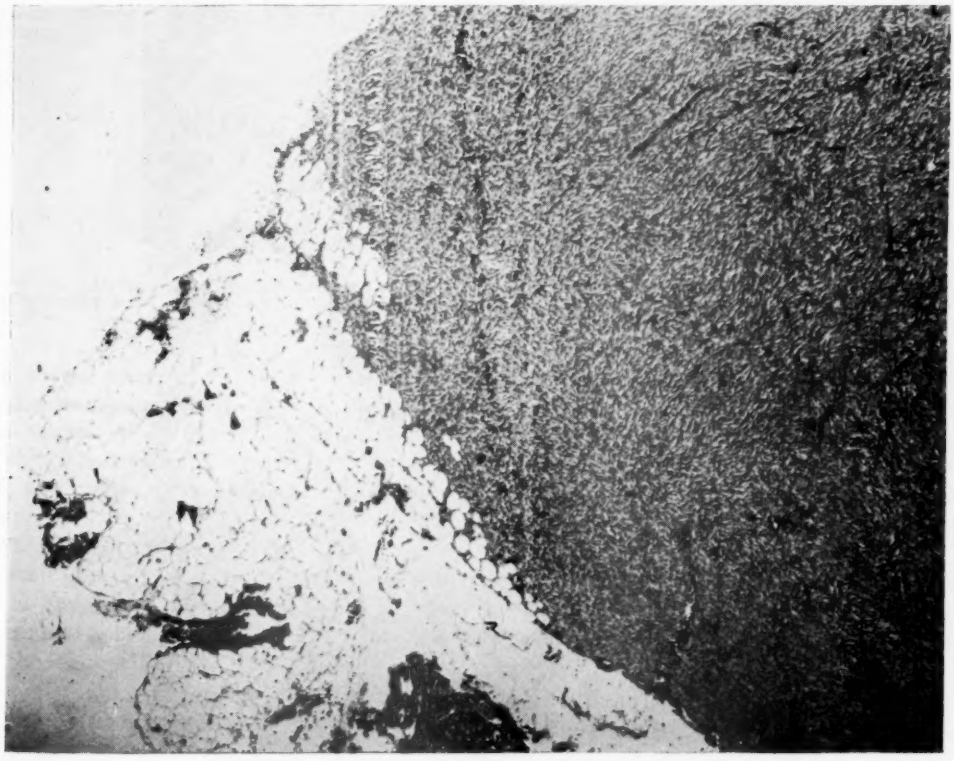

Fig. 3 (Case 1).—Same slide as Fig. 1 demonstrating the invasion of fatty tissue by the tumor at the lowermost extent of the lesion. (×52.)

two palpable masses were readily excised and were found to be firm and well encapsulated. The pathologic report was dermatofibrosarcoma. Histologically, the tumors were found to be quite cellular with spindle-shaped to oval nuclei present in current and eddy formation. There was a mild irregularity in the staining characteristics of the nuclei. An occasional mitotic figure was noted.

The patient was readmitted on April 15, 1946, because of a recurrent mass at the same site of 2 months' duration. System review was negative. The abdominal wall tumor was about 1 inch in diameter and was somewhat to the right of the epigastric region. On April 22, 1946, under local anesthesia, the tumor mass, together with a portion of the anterior sheath of the right rectus muscle, was excised. The pathology report was dermatofibrosarcoma protuberans.

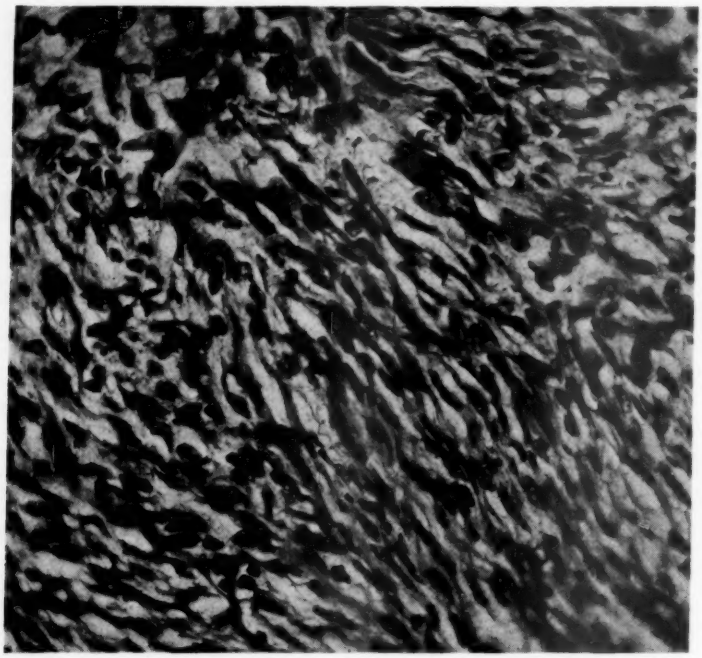

Fig. 4 (Case 1).—High-power magnification of tumor showing cellular detail. A clump of dark chromatin material may be seen at almost the exact center of the field representing active mitosis. (×475.)

The patient was seen again on Nov. 9, 1948, with a recurrence. System review and chest x-ray were negative. On examination, there were two firm, nontender masses about the size of marbles above and below the midpoint of the abdominal scar. These masses were freely movable under the skin, but appeared fixed to the deep structures. On Nov. 17, 1948, the recurrent tumors were excised under general anesthesia. The pathology report was dermatofibrosarcoma protuberans.

The patient's most recent admission was in June, 1951, with a recurrence in the scar of 6 months' duration. System review was negative. On examination, a 1 cm. subcutaneous nodule was found to be present in the left extremity of the abdominal scar to the left of the umbilicus. This nodule was freely movable and nontender. It was excised under local anesthesia on June 20, 1951. The pathology report was dermatofibrosarcoma protuberans.

In summary, then, this patient's lesion first appeared 29 years ago. Since its first appearance, the patient has had nine excisions of the initial lesion and eight recurrences. Six of these procedures have been done at this institution. The longest interval was 14 years between the first and second recurrences. The patient's general health and well-being are otherwise excellent.

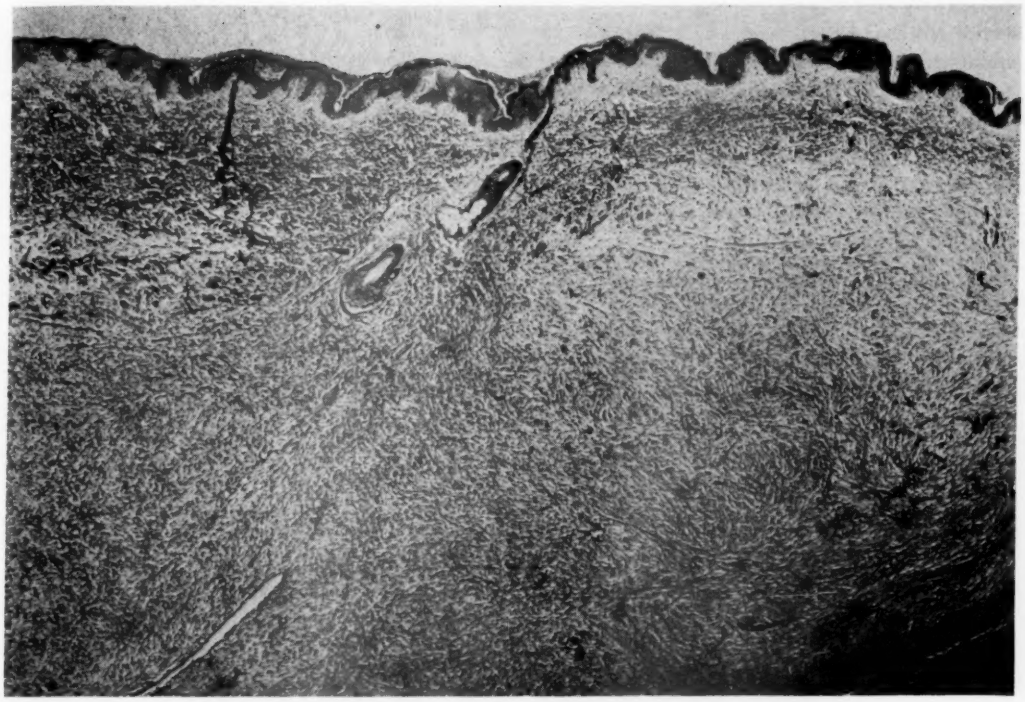

Fig. 5 (Case 2).—Low-power view of tumor showing relationship to the overlying epidermis. Compare with Figs. 1 and 2 and note that this lesion is poorly demarcated from the corium. (×52.)

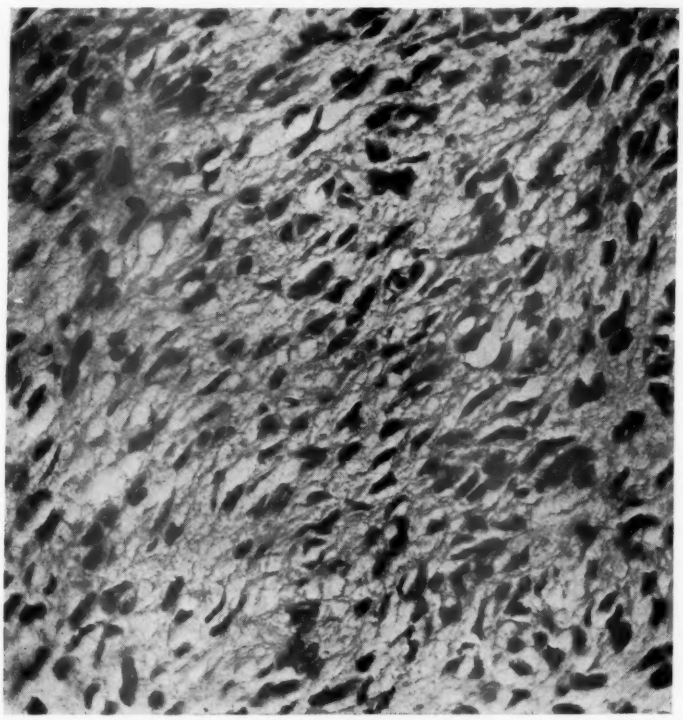

Fig. 6 (Case 2).—High-power magnification of tumor showing cellular detail. (×475.)

CASE 2 (Register No. 113823).—R. J. L., a 32-year-old white man, was admitted to the Bronx Veterans Administration Hospital for the first time on March 11, 1949, with a chief complaint of a tumor of the left anterior chest wall of 2 years' duration. The patient stated that in 1944, while unloading rations from a freight car, he bruised the skin of the left chest region. The patient did not notice any swelling in this area at that time. In 1946, the patient had a second traumatic impact to this same area, and subsequently noted the gradual development of a swelling in this area, together with a sense of discomfort locally. The patient saw his family physician who recommended surgical excision.

Fig. 7 (Case 3).—Low-power view showing relationship of tumor to the epidermis. Here, again, there is poor demarcation between corium and tumor. Note the invasion of fatty tissue by the tumor at the depth of the lesion. (×52.)

Physical examination revealed a small palpable mass about 4 cm. in diameter on the left anterior lower chest wall with a slight bluish discoloration of the overlying skin. There were no enlarged lymph nodes. Chest x-ray was negative. On March 16, 1949, the mass was

excised under local anesthesia, and the wound was closed per primam. The pathology report was dermatofibrosarcoma protuberans. Microscopic examination of the edges of the excised specimen revealed no tumor, indicating an adequately wide excision. The wound healed per primam. Attempts to have the patient return to the Follow-Up Clinic have been unsuccessful to date.

CASE 3 (Register No. 129429).—L. C., a 36-year-old white man, was admitted to the Bronx Veterans Administration Hospital for the first time on June 19, 1950, because of a "lump" on his back. The history dated back to 1937 when the patient fell and bruised his low back region. Following this injury, a flat, red mark approximately 2 cm. in diameter developed at the site of impact. This remained asymptomatic and stationary until about 1 month prior to admission when it began to enlarge and became raised above the surface. Two days prior to admission, the patient consulted his family doctor who felt that the lesion represented an abscess, and incised it. No pus was obtained, but a considerable amount of bleeding ensued with increasing soreness of the lesion. The patient was referred to the hospital for further management.

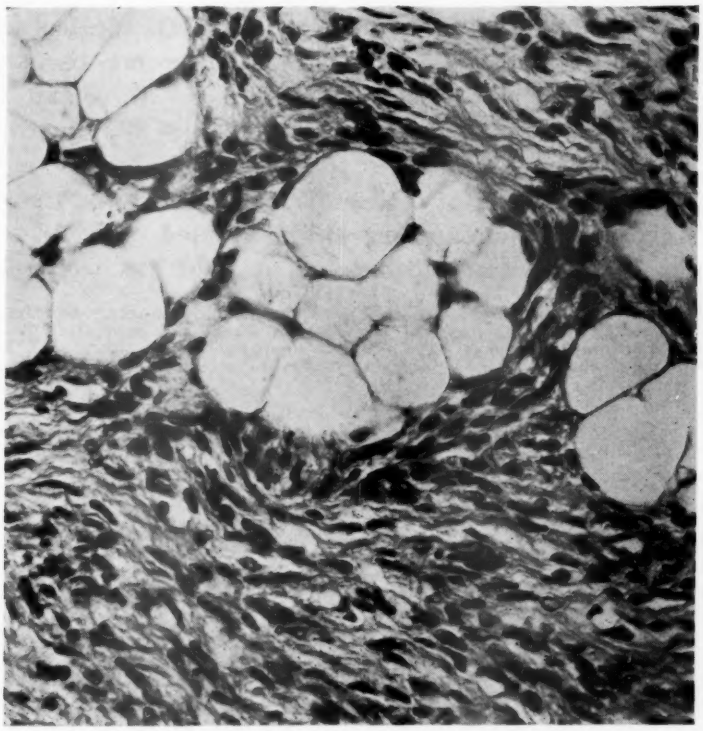

Fig. 8 (Case 3).—Cellular detail of tumor showing invasion of fatty tissue by tumor cells. (×475.)

Physical examination revealed a mass 4 cm. in diameter in the lumbar region to the right of the midline, with a central incision and active bleeding. The mass had a bluish discoloration, was hard in consistency and rounded. There was no lymphadenopathy. A preoperative diagnosis of hemangioma was made and, on July 24, 1950, under local anesthesia, the lesion was excised from the back with a wide circular incision extending down through skin and subcutaneous tissue to muscle fascia. A sliding flap type of closure was effected. The pathology report was ulcerated dermatofibrosarcoma protuberans. Microscopic examination of the peripheral portions of the excised specimen indicated incomplete removal in one of the sections laterally. Therefore, on Aug. 16, 1950, a secondary excision was carried out with complete excision of the previous operative area and application of a split-thickness

graft. The graft did not completely take and required the application of a small second graft on Sept. 6, 1950. Pathologic examination of the second excised specimen revealed no evidence of tumor. The wound healed uneventfully. The patient was last seen in the Follow-Up Clinic on April 12, 1951 (8 months following surgery), at which time no recurrence was noted, and no lymphadenopathy was present.

SUMMARY

1. The significant literature and the important clinical and pathological features of dermatofibrosarcoma protuberans are reviewed.

2. The protuberant character of these lesions grossly is noted.

3. This lesion may be considered to be intermediate in position between fibroma and sarcoma just as basal-cell epithelioma is intermediate in position between benign epithelial growths and squamous-cell carcinoma. Dermatofibrosarcoma protuberans also resembles basal-cell carcinoma in its tendency to recur locally and metastasize only very rarely.

4. The treatment of choice is adequate, complete, surgical excision which should include several centimeters of surrounding normal tissue together with the fascia overlying the muscle deep to the lesion. In certain instances, the resultant wound may be extensive enough to require skin grafting.

5. The accurate interpretation of the historical, physical, and histological findings is especially important when this lesion occurs on the extremities so that unnecessary radical amputations will be avoided.

6. Three cases of dermatofibrosarcoma protuberans are presented.

The author wishes to acknowledge the kind assistance rendered by Dr. A. Liber of the Department of Pathology of this hospital who helped select representative fields of the microscopic slides for photomicrography. The author also wishes to thank Dr. M. J. Healy, Jr., of the Department of Surgery, for his many valuable suggestions.

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THE PRESERVATION OF BONE GRAFTS BY FREEZE-DRYING

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BONE grafts, preserved by freeze-drying, have been experimentally transplanted in dogs as reported by Kreuz, Hyatt, Turner, and Bassett.[1] The material when grafted appears to be incorporated in the same manner but at a slightly slower rate than fresh autogenous bone grafts. The freeze-dried bone appears to be slightly superior to frozen bone in rate of healing. The freeze-dried grafts are incorporated in a manner which compares favorably to the same sized bone defect. Further, the freeze-dried material may be stored and shipped at room temperature over long periods of time. In short term (one year) follow-up of four patients there is evidence of initial acceptance and incorporation by the host bone of this type of stored bone.

Orthopedic casualties resulting from acts of war are once again a most serious problem. The interest of the orthopedic surgeon in preserved bone becomes readily evident when the operator finds he is not forced to accept the added responsibilities of another operative incision with the increased operative trauma to both bone and soft tissue, the possible prolongation of operative time, the discomforts often attendant on a chronically painful donor site, and the occasional fracture that follows graft removal from the usual sites of the tibia. However, the clinical use of any stored bone should be dictated by reasonable surgical indications. Even the best method of preservation should not be considered the equal of fresh autogenous grafts.

The prime indications would seem to be those associated with extensive bone replacement during the course of reconstructive orthopedic procedures. Other uses include filling cavities formed by bone cysts, defects left by removal of large tumors, and as added osteosynthetic and osteogenetic factors to fresh autogenous grafts, for example, in spine fusions of the Hibbs type. In military surgery, particularly at the battle front, the use of preserved bone for fresh fractures, usually compounded, is rarely indicated because of the dangers of infection with resultant osteomyelitis.

Until the proper evaluation of all types of preserved bone is completed by responsible groups extreme caution should be exercised in the use of any stored bone. The excesses followed by assuredly poor results may greatly impede the general acceptability of a fundamentally worth-while process. In our opinion, the current advancement of freeze-drying, while definite and noteworthy, is still in the field of clinical research. The specialized method used for freeze-drying these preparations is presented here.

The specific objectives gained by freeze-drying the bone as contrasted with other possible methods of drying are: First, the temperature is below that

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at which labile components undergo chemical change. Second, bubbling or foaming of liquid content does not occur, thus avoiding surface denaturation of proteins that otherwise occurs above freezing even though the temperature may be relatively low. Only the frozen state can prevent this. Third, the solute contained in liquid in the bone remains evenly dispersed and distributed, undergoing no concentration as the frozen solvent sublimes. There is no reduction in space occupied. Fourth, because of the "locked" condition of molecules of solute there is no coagulation of even lyophobic sols. Even with lipoidal components there is no more than a slight degree of turbidity and far from complete coalescence. Fifth, there is no "case-hardening" so that a lower content of moisture for greater stability can be obtained than with any other method of drying. Sixth, and of particular importance is the fact that no bacterial growth or enzymatic change can take place under the frozen conditions of drying or during final storage and transportation. The importance of this for preservation of asepsis cannot be overemphasized for graft surgery.

The history of freeze-drying in general, basic underlying principles, previous applications, and type of equipment used have been set forth in detail.[2] The following is a description of the specialized process of freeze-drying the grafts. This method as now developed for fresh bones may be described briefly as one of prefreezing at about −20° C. (or preferably at lower temperature, if available) and encasing in an ice block followed by forced rapid drying under high vaccum from the frozen state. To sublime the ice, the frozen bone has heat applied to it rapidly within a vacuum chamber but without melting and the vapors in the high vacuum are rapidly removed, either by condensation at low temperature or in a chemical desiccant in standard equipment previously described.[2] For smaller scale laboratory work, manifold types of equipment may be used. The final completely dried bone must then be hermetically sealed in a container for storage and distribution. This container preferably should be one which is vapor-proof and can be readily opened by the clinician aseptically.

The latent heat of sublimation must be supplied to the grafts rapidly in order to complete the drying in a minimum of time. However, this also means there must be free and rapid sublimation so that the loss of heat as a result of the sublimation is rapid enough to be in balance with the rate at which it is supplied. This is accomplished readily in other applications from frozen solutions, particularly of protein such as blood plasma, where an open porous spongelike matrix is obtained as drying proceeds. Ready diffusion of water vapor for this reason takes place from the ice surface after it has receded by evaporation to well under the original outside surface. By contrast, rapid evaporation and diffusion through dense bone surface without localized thawing is considerably more difficult to achieve. Accordingly, other means must be utilized to hold the temperature uniformly low and yet allow forced heating and drying. To this end, the bone, after it has been first frozen, is encased in a solid block of ice.

There are three ways to handle the bone for carrying out freezing and drying: (1) it may be placed in individual containers as is done with individual

doses of blood plasma, (2) it may be handled in bulk in large bottles, or (3) it may be handled in bulk in sterility trays, followed by aseptic transfer into individual containers as is done with antibiotics like streptomycin.

If individual bottle sare used, the frozen bone is encased in a block of ice by placing it on a 3 mm. thick ice slab made from sterile distilled water in the container held at low temperature. At intervals the frozen bone is sprayed with cold, sterile, distilled water. Care must be exercised not to spray more water at one time than can be done without melting of the surface of the frozen bone itself. After this layer has been built up to a thickness of 2 or 3 mm., layers of water a few millimeters thick are added one at a time to encase the bone gradually in a block of ice.

If multiple frozen bone sections are processed in bulk in large bottles, the ice block is produced as a shell half way around the inner periphery. The block of ice otherwise is built up in the same manner.

Where large numbers of grafts are being dried, the procedure just outlined with individual containers, even with multiple grafts in large bottles, becomes quite laborious and cumbersome. This is parallel to what has been encountered in drying antibiotics on a large scale. For this reason, large numbers of grafts are handled in stainless steel trays with sterility lids. The sterility lids are so designed as to permit the ready outflow of water vapor required for the high vacuum conditions and at the same time to prevent contaminants from getting into the trays.[2] Otherwise, the procedure for building up the ice block is the same. When processing in bulk, the final dried bone grafts are transferred to suitable glass containers according to standard practice[2] using a surgical type of technique as is done with antibiotics.

All final containers for storage and distribution are sealed with rubber stoppers under vacuum, using standard equipment. Aluminum cap seals may be used or the rubber stoppered glass containers may be hermetically sealed under vacuum in cans as in the current practice with blood plasma for military purposes, or in a collapsible type of tubes.[2] At the time of use, these containers lend themselves readily to reconstitution of the grafts aseptically with saline or plasma or other fluid or for removal from the container dry to reconstitute in situ following completion of the operative procedure.

These several procedures may be applied to cancellous bone, cortical bone, or ground bone. As indicated, this procedure has proved itself as an excellent aseptic technique in the many thousands of parenteral injections made with blood plasma and other preparations during the past ten years. However, at some of the contemplated locations where it may be necessary to carry out graft surgery, conditions may not necessarily be favorable for asepsis. The container with freeze-dried bone grafts, just as with frozen grafts or fresh graft, may be sterile as opened but subsequent contamination can occur. For this reason, it may be advisable to take advantage of the freeze-drying process to incorporate an antibiotic such as penicillin. To accomplish this, the antibiotic is placed in the first one-millimeter layer of ice as built up by spraying a solution of it in sterile distilled water on the frozen bone. Concentrations up to 100,000 units per c.c., approximately, are in order. During reconstitution, this penicillin is

carried into the bone itself as the fluid is absorbed. Also, some remains on the surface. The antibiotic is particularly effective where reconstitution takes place in situ after completion of the operative procedure. To summarize, by use of the freeze-drying process, advantage can be taken of an additional precaution to assist in preventing contamination.

SUMMARY

Freeze-drying of bone grafts provides an excellent means of storage and transportation under adverse conditions. A procedure of encasing frozen bone in an ice block and drying under high vacuum without melting is described. The method lends itself particularly to maintaining a sterile product.

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COMPARATIVE UTILIZATION OF INTRAVENOUS INVERT SUGAR AND GLUCOSE

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RECENT reports[4-6] stating that invert sugar and fructose are utilized more efficiently than glucose by the human being when administered by intravenous injection led us to conduct the investigations reported in this paper. It would appear important to determine whether or not these substances are superior to glucose, as glucose is so widely used clinically in parenteral alimentation.

METHODS

Patients on the surgical wards of the Wadsworth Hospital, Veterans Administration Center, Los Angeles, were studied. They were adult men within the age range of from 20 to 50 years, who had not been operated upon and who were not suffering from any obvious nutritional deficiencies. Before the patients were given infusions, a glucose tolerance test was performed. On the day following this test, a 24-hour collection of urine was obtained and analyzed for total reducing substances. On the day that the infusion was to be given, the bladder was emptied, a fasting blood sample obtained, and the 24 hour urine collection begun. One group of 10 patients received 10 per cent invert sugar in distilled water, and another group of 10 patients received 10 per cent glucose in distilled water. Oral intake was not restricted. One liter infusions were given each day for three days. The rate of infusion was regulated so that the injection required two hours the first day, four hours the second day, and six hours the third day. A fasting blood sugar level was obtained each morning prior to the administration of the solution.

Another group of 11 patients was then studied. A 24 hour collection of urine was obtained during which time water but no food was allowed to be taken orally. A glucose tolerance test was performed. After midnight all oral intake was withheld. At 8 A.M. a fasting blood sugar level was obtained, and the bladder emptied. Five patients were given an infusion of 10 per cent invert sugar in distilled water, and 6 patients were given an infusion of 10 per cent glucose in distilled water, both groups receiving the injections over a 2 hour period. During the 24 hour period of urine collection, these patients received water by mouth but no food.

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Urine collections were analyzed for total reducing substances by the method of Somogyi and for sodium and potassium on a Weichselbaum-Varney flame spectrophotometer.

RESULTS

It was noted that the retention of both invert sugar and glucose increased as the period of infusion was lengthened from 2 to 6 hours. There was considerable variation in the amount of excretion of reducing sugar in both groups of patients, but in both groups the retention of glucose was significantly greater than that of invert sugar (See Tables I and II). When the infusions were of

TABLE I. TOTAL REDUCING SUGAR IN 24 HOUR URINE COLLECTION FROM PATIENTS RECEIVING 1 LITER SOLUTIONS OF 10 PER CENT GLUCOSE, NONFASTING (IN GRAMS)

PATIENT	24 HR. CONTROL, NO INFUSION	2 HR. INFUSION	4 HR. INFUSION	6 HR. INFUSION
1	2.19	10.82	6.20	5.30
2	5.40	6.17	4.85	6.42
3	0.92	13.09	2.20	2.35
4	0.96	7.66	4.89	4.76
5	1.75	13.72	10.26	5.16
6	0.80	10.24	8.47	6.16
7	0.80	6.21	2.27	2.29
8	0.70	8.82	6.00	5.37
9	1.36	7.02	6.84	5.48
10	2.19	9.30	6.20	5.50
Average	1.70	9.30	5.82	4.88
	Per cent of Retention During the 24 Hour Period			
		90.70	94.18	95.12

TABLE II. TOTAL REDUCING SUGAR IN 24 HOUR URINE COLLECTION FROM PATIENTS RECEIVING 1 LITER INFUSIONS OF 10 PER CENT INVERT SUGAR, NONFASTING (IN GRAMS)

PATIENT	CONTROL, NO INFUSION	2 HR. INFUSION	4 HR. INFUSION	6 HR. INFUSION
1	2.44	12.96	20.70	14.52
2	1.99	28.20	20.29	8.36
3	6.12	10.64	10.50	7.48
4	3.60	4.55	3.85	12.10
5	2.39	19.50	11.10	11.40
6	11.06	46.96	32.22	22.38
7	1.74	39.29	27.09	24.00
8	4.41	13.69	14.29	7.74
9	0.85	18.03	13.12	11.65
10	1.76	29.60	30.07	11.80
Average	3.64	22.34	18.32	13.14
	Per Cent of Retention During the 24 Hour Period			
		77.66	81.68	86.86

2 hours' duration, 13.04 Gm. more of reducing sugars appeared in the 24 hour collection of urine in the group receiving invert sugar than in the 24 hour collection from the group receiving glucose. A difference of 12.2 Gm. was noted in patients receiving infusions over a 4 hour period, and the 6 hour infusion resulted in a difference of 7.77 Gm. Because the oral intake of the patients in the first group of experiments was not assayed and might have influenced the results obtained, a second experiment was conducted and the group was allowed

to have no food during, and for 24 hours preceding, the period of urine collection. Again the group receiving invert sugar lost an average of 7.15 Gm. of reducing sugar more than the patients receiving glucose. There appeared to be no significant difference in the excretion of sodium and potassium between the patients receiving glucose and those receiving invert sugar (See Tables III and IV).

TABLE III. ANALYSIS OF 24 HOUR URINE COLLECTION FROM PATIENTS RECEIVING 1 LITER INFUSIONS OF 10 PER CENT INVERT SUGAR, FASTING*

	CONTROL PERIOD—NO INFUSION				INFUSION PERIOD			
PATIENT	URINE VOLUME	GM. SUGAR	MEQ. Na	MEQ. K	URINE VOLUME	GM. SUGAR	MEQ. Na	MEQ. K
1	1,507	1.73	130.4	47.5	1,820	13.46	160 0	67.4
2	1,000	1.36	116.7	38 7	1,150	7.20	147.9	58.6
3	550	0.80	97.6	15.9	1,600	10.24	120.7	42.7
4	850	0.96	103.8	29.8	1,110	8.24	216.9	107.9
5	1,400	2.24	146.1	39.6	1.362	12.80	184.7	97.6
Average	1,061	1.42	118.9	34.3	1,408	10.38	166.0	74.8

*Water but no food by mouth.

TABLE IV. ANALYSIS OF 24 HOUR URINE COLLECTION FROM PATIENTS RECEIVING 1 LITER INFUSIONS OF 10 PER CENT GLUCOSE, FASTING*

	CONTROL PERIOD—NO INFUSION				INFUSION PERIOD			
PATIENT	URINE VOLUME	GM. SUGAR	MEQ. Na	MEQ. K	URINE VOLUME	GM. SUGAR	MEQ. Na	MEQ. K
1	1,200	1.20	159	62	2,900	3.19	150	56
2	3,100	2.17	142	61	3,800	4.59	130	79
3	1,200	1.56	167	70	1,800	2.49	156	76
4	1,550	1.86	181	80	1,600	2.30	158	84
5	4,000	0.42	173	93	3,600	3.99	169	91
6	1,150	0.83	164	80	1,200	1.68	152	97
Average	2,033	1.34	164	74.3	2,483	3.04	152.5	80.5

*Water but no food by mouth.

DISCUSSION

It would appear that under the conditions reported in this paper glucose injected intravenously is better retained in human beings than is invert sugar. Glucose is the only hexose known to be reabsorbed from the glomerular filtrate in any significant quantity.[3] In order for fructose, which comprises half of invert sugar, to be retained to any appreciable degree, it would be necessary that it be removed from the circulation quite rapidly, presumably by conversion to glycogen, in order not to be lost in the urine. Although fructose appears to be converted to glycogen more rapidly than glucose, it has also been demonstrated that after the oral ingestion of small amounts of fructose, it appears in the urine despite the blood fructose level remaining quite low.[1] Woodyatt and associates[8] found a lower tolerance for fructose than for glucose when the sugars were administered by constant intravenous injection.

The reasons for the discrepancy between our findings and those reported elsewhere[4, 5] are not clear. Even if fructose were retained to a greater degree than glucose, it does not seem that there should be a very marked difference between the retention of 10 or 15 per cent invert sugar and 10 per cent glucose. A solution of 10 per cent invert sugar must actually be considered as a solution

of 5 per cent glucose containing 5 per cent fructose. The reports of Weinstein[4, 5] are based on urine collections continued for three hours after the injection of invert sugar has been completed. It may be that significant additional quantities of sugar appear in the urine after this time, thus accounting, at least in part, for the difference found in our results, which were based on 24 hour urine collections. It would appear that further studies are needed to determine to what degree fructose is utilized in the human being. These studies should include investigations of retention after repeated administrations as well as determination of retention after single injections.

SUMMARY

A greater quantity of reducing sugar appeared in the urine which was collected over a 24 hour period from patients receiving one liter infusions of 10 per cent invert sugar than from those receiving 10 per cent glucose. This was noted in patients who received oral feedings as well as in those from whom food was withheld. It would appear dubious that invert sugar or fructose is as well utilized by the human being as is glucose.

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COLLATERAL ARTERIAL CIRCULATION TO THE LIVER OF THE DOG

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OBSERVATION by ourselves, as well as by others, that complete ligation of the hepatic arterial blood supply without administration of antibiotics does not necessarily cause serious damage to the liver, nor death in all instances, is of more than academic interest. After reviewing the literature on the subject, our interest was stimulated to investigate whether the collateral arterial circulation to the liver might explain the phenomenon.

In 1906, Haberer[1] investigated the hepatic arterial blood supply and concluded that the anatomy of the hepatic artery in man, dog, and cat are similar; in these species, ligation of the hepatic artery at the celiac axis can be done without fear of liver necrosis and will not interfere with normal arterial blood supply to the liver; ligation beyond the right gastric or the gastroduodenal arteries is dangerous and may lead to liver necrosis in the case of a normal anatomy of the celiac arteries; however, in case of disease of the hepatic artery, such ligation is permissible, because collateral circulation will exist. He mentioned the importance of collateral blood supply from the phrenic arteries.

In 1950, Ellis and Dragstedt[2] demonstrated that gas gangrene produced by ligation of the hepatic arterial supply was due to diminution of oxygen supply of the liver, which allowed for growth of anaerobic organisms that are nearly universally present in adult animals. Their observations were confirmed by Markowitz and co-workers[3] who showed, in addition, that penicillin could inhibit anaerobiosis and consequently prevent the production of gas gangrene and death.

More recently, Tanturi and associates,[4] and Grindlay and associates[5] have written on the subject, but they do not explain adequately the normal appearance of livers in animals surviving complete ligation of the hepatic arteries. It appears that in the surviving animals, the collateral arterial supply enters the liver by way of diaphragmatic arteries and by arteries along the portal vein, the vena cava, and the common bile duct. However, no systematic demonstration of this assumption could be found. The literature has been reviewed recently by Markowitz.[6]

EXPERIMENTAL METHOD

Thirty-six normal healthy male and female mongrel dogs were divided into three groups, and were operated upon using pentobarbital sodium anesthesia and aseptic technique. All dogs were on a diet containing horse meat, bread, and

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hospital scraps. The anatomy of the vascular tree in the dog and the extent of excision of arteries are demonstrated in Fig. 1. The schematic drawing represents our findings in 20 normal animals and in the experimental animals reported presently.

In 6 animals, the hepatic arterial trunk was ligated and in 30 animals it was excised completely from the celiac axis to the terminal branches at the hilum of the liver, including the gastroduodenal, right gastric, and cystic arteries, as well as accessory branches of the hepatic arteries (Fig. 2).

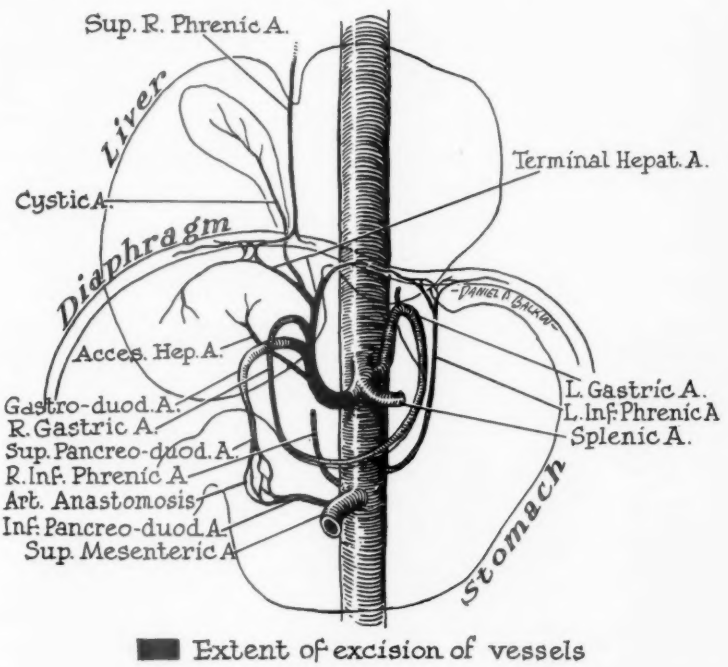


Fig. 1.—Diagram of arterial supply to dog's liver, indicating observed collaterals.

First Group, 10 Dogs.—Eight animals were given a single dose of 300,000 units of penicillin in oil and one gram of streptomycin by intramuscular injection immediately following the operation. Two dogs were given one gram of terramycin* daily by mouth for one week following the operation.

Second Group, 16 Dogs.—No antibiotic drugs were given.

Third Group, 10 Dogs.—An additional cholecystectomy was done. No antibiotic drugs were given.

Surviving animals were sacrificed 3 to 172 days following operation. In all animals, the thoracic aorta was injected with a commercial red lead dye injection fluid† and a careful examination and dissection were made of the entire hepatic system. None of the ligated arteries were found to have recanalized.

*The terramycin was kindly furnished by Dr. W. A. Wright of Chas. Pfizer & Co. Inc., Brooklyn, N. Y.

†The red lead dye used was kindly furnished and its use demonstrated by Mr. Walter D. North of the Demonstrator's Association of Illinois, Chicago, Ill.

RESULTS

In the first group of 10 dogs treated with antibiotics, none died. Four of these animals showed a direct communication between the inferior or superior phrenic arteries, or both, and the extrahepatic liver arteries. The red lead dye could be traced from the phrenic arteries directly into the hepatic arteries in the liver. All dogs showed a filamentous arterial supply to the liver along the vena cava and the common bile duct.

In the second group of 16 dogs, without antibiotic therapy, 8 died from 24 to 72 hours following operation with foamy liver or hemorrhagic peritonitis or both. In none of the animals which died could a vestige of collateral circulation be demonstrated, particularly between the inferior phrenic arteries and the liver. The remaining 8 dogs, when sacrificed, showed excellent collateral communications between the inferior or superior phrenic arteries or both, and the hepatic arteries in the liver (see Figs. 1 and 3). Also, a filamentous arterial supply to the liver could be demonstrated along the vena cava and the common bile duct.

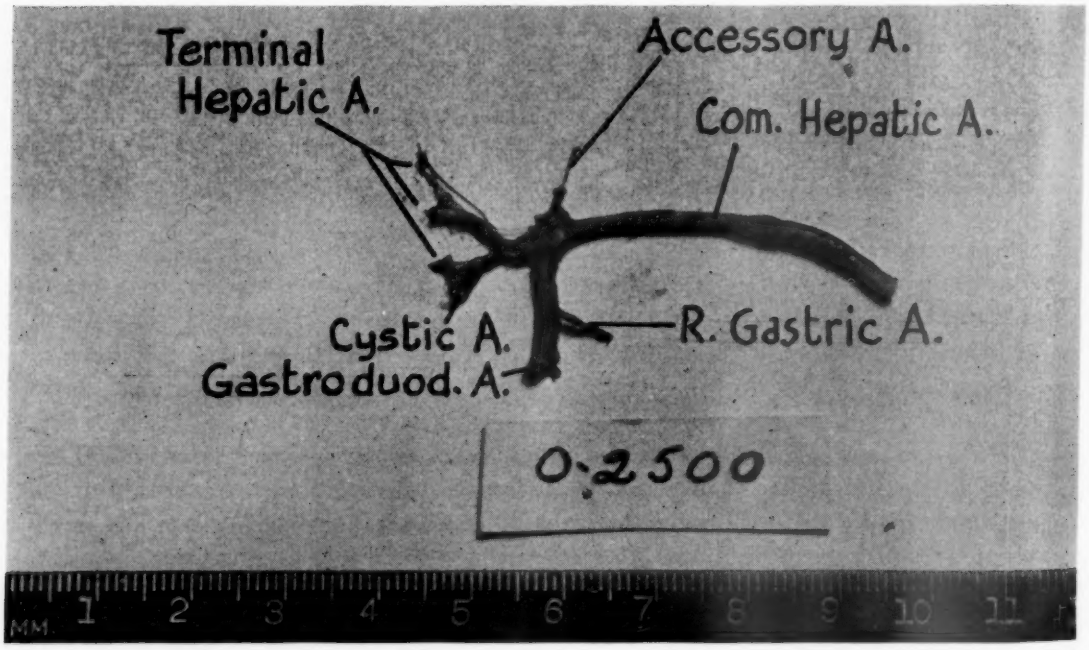
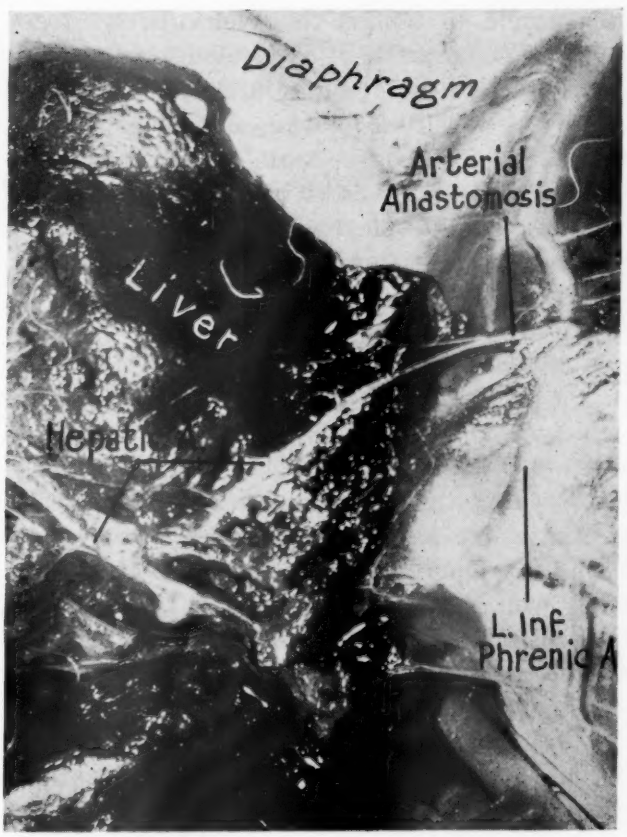


Fig. 2.—Specimen from a dog operated upon, showing the extent of excised arterial trunk.

In the third group of 10 dogs, without antibiotic therapy, 8 died with foamy liver or hemorrhagic peritonitis or with both. No vestige of collateral circulation could be demonstrated in any dog which died. The 2 dogs that survived had an excellent communication between the inferior or superior phrenic arteries or both and the hepatic arteries. The filamentous arteries along the common bile duct were obscure and minimal.

In the group of 30 dogs in which the arterial hepatic trunk was excised, 26 were found to have accessory or aberrant hepatic arterial branches which

A.



B.

Fig. 3, *A* and *B*.—Injected specimens of two different dogs, showing frequency of direct anastomoses between hepatic and left inferior phrenic arteries.

emerged from the common hepatic trunk about 1 to 2 cm. distal to the celiac axis: 5 dogs had two accessory arteries each, and 21 dogs had one accessory artery each.

Of the total number of 36 dogs, 2 animals in the second group of experiments developed perforations of the gall bladder. The perforations were walled off with omentum and liver and were plastered against the diaphragm. One of these animals had a slight bile peritonitis, but neither appeared ill as a result of the perforation during 2 to 8 weeks of observation. Shrunken, thickened, and atrophic gall bladders were found in other dogs without evidence of necrosis. Some liver necrosis and infarcts were observed in dogs which survived with antibiotics and which had no evidence of a good collateral arterial blood supply to the liver. The animals which survived without antibiotics showed an excellent collateral arterial blood supply and there was no clinical or gross evidence of hepatic necrosis.

DISCUSSION

In view of the literature and of our own results presented above, we can state that the mere term "ligation of the hepatic artery" means nothing unless it is stated exactly where the ligation was performed, and whether accessory arteries supplied blood to the liver. It can be seen readily that it is not easy, if at all possible, to deprive the liver entirely of its oxygen supply. However, the degree of deprivation of oxygen supply surely must play a role. This may explain the widely divergent results on survival in case of ligation of the arterial supply to the liver in man, as well as in the dog. It is also quite evident that survival of dog or man, following ligation of the hepatic artery, will depend on factors unknown at the time of operation, such as accessory hepatic arteries and the degree of supply from the phrenic arteries. This is extremely hard to ascertain at the operating table as shown in our experiments, where only with the injection method such branches could be detected.

Another question arises from our results, namely, why so many good experimenters did not evaluate the importance of the collateral circulation properly, particularly from the phrenic artery. Only Haberer[1] and Huggins and Post[7] have stressed this point. In other papers, it was mentioned only occasionally, or it was investigated in only a few animals. Most investigators injected through the celiac axis or the hepatic artery. In this case, other communications like the filamentous arteries along the portal vein and along the cystic duct, as well as the anastomosis of the hepatic artery with the phrenic artery may be missed.[7] To our knowledge, only Haberer has injected the hepatic arterial tree systematically in dog and in man through the aorta. The injection material used may be decisive for the demonstration of all collateral arteries. If it is too viscid, it will enter only the larger branches.

In man, dog, and cat, according to the best information we could obtain from the literature, and in man and in dog, according to our own experience, the ramification of the celiac axis and the collateral supply of arterial blood to the liver are similar. We believe, therefore, that our results on the dog can

be applied to conditions in man. It may be possible to demonstrate in man on the operating table the presence or absence of collateral supply to the liver with the use of the fluorescein method described in earlier papers from our laboratory.[8] This may answer the question whether the hepatic artery in man may be ligated with impunity during an operation.

Apparently the liver in man and in the dog needs a certain degree of arterial blood. This need may vary with the activity of the liver and possibly other conditions unknown as yet. We may conclude from our results, however, that complete ligation of every arterial supply to the liver through the hepatic artery and collaterals will lead to necrosis of the liver and death in the dog, as well as in man. The mechanism of death in dog and man seems to be different, however. In the dog, as soon after birth as the intestinal tract is inhabited by bacteria, liver and pancreas seem to become infested, particularly with gas-forming rods. These gas-forming bacteria, similar to *Clostridium welchii,* seem to be suppressed by the presence of a certain amount of oxygen. It is not entirely clear in our minds, however, that this is the sole cause of death following ligation of arterial blood supply to the liver because, depending on physiologic variations, the portal vein may carry a considerable amount of oxygen to the liver. It has been shown by Markowitz and co-workers[3, 6] that dogs can be saved following more or less complete ligation of the hepatic arterial supply by the administration of antibiotics. Such experiments, however, do not tell the whole story because a number of dogs in our own experiments, and in experiments of others, following ligation of arterial supply to the liver, survive without the use of antibiotics. In our dogs that survived, we found the existence of sufficient collateral circulation to explain their survival. We may assume that in man, similar conditions may prevail if complete ligation of the extrahepatic liver arteries has been performed. In that case, survival seems to depend entirely on collaterals which may be hidden.

We conclude that in the dog a number of anastomoses, particularly through the left phrenic artery, supply so much arterial blood to the hepatic arterial circulation of the liver, that complete ligation of all extrahepatic liver arteries may not be sufficient to lead to liver necrosis and death.

SUMMARY AND CONCLUSIONS

Complete excision of the hepatic arterial trunk appears to us to be the only way to assure complete occlusion of the hepatic artery because of the aberrant or accessory branches which are usually present and which may otherwise be overlooked.

Antibiotics such as penicillin and terramycin can protect animals against death from complete excision of the hepatic arterial trunk.

A number of animals can survive complete hepatic arterial excision without antibiotics providing they have adequate collateral circulation from the phrenic arteries.

Cholecystectomy at the time of operation adds considerably to the morbidity and mortality, largely by abolishing the filamentous arterial supply along the common bile duct.

Collateral arterial circulation to the liver can be demonstrated with certainty only if the aorta itself is injected with dye.

The inferior or superior phrenic arteries are capable of sustaining an adequate arterial blood supply to the liver. When such collateral anastomosis is present, antibiotics are not necessary.

We have not been able to demonstrate adequately this collateral circulation at the time of operation.

At no time were we able to demonstrate a collateral arterial blood supply to the liver from the upper branches of the left gastric artery, left superior phrenic artery, or esophageal arteries.

The collaterals as demonstrated by us were the left inferior phrenic, right inferior phrenic, and the right superior phrenic arteries, in the order of frequency as named.

Since the anatomy of the extrahepatic arteries in man and dog is similar, we believe these data may be useful in clinical surgery in man.

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A HIP SPICA PLASTER APRON TO PREVENT WITHDRAWAL OF CATHETER BY IRRATIONAL PATIENT

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(From the Charity Hospital of Louisiana)

A SIMPLE and effective hip spica plaster apron has been devised for use in preventing irrational patients from removing their indwelling catheters. Occasionally irrational patients in hip spica casts also require an indwelling catheter for their treatment and will remove their catheters, causing considerable urethral trauma and opening new avenues for infection. The usual admittedly inadequate methods of preventing this are the use of arm restraints and special attendants. A hip spica apron greatly simplifies this problem.

A suprapubic cystotomy is sometimes necessary in the urological patient because of complications following such traumatic removal of catheters. The application of a double hip spica cast to the knees with the plaster apron added would be preferable to such surgical treatment.

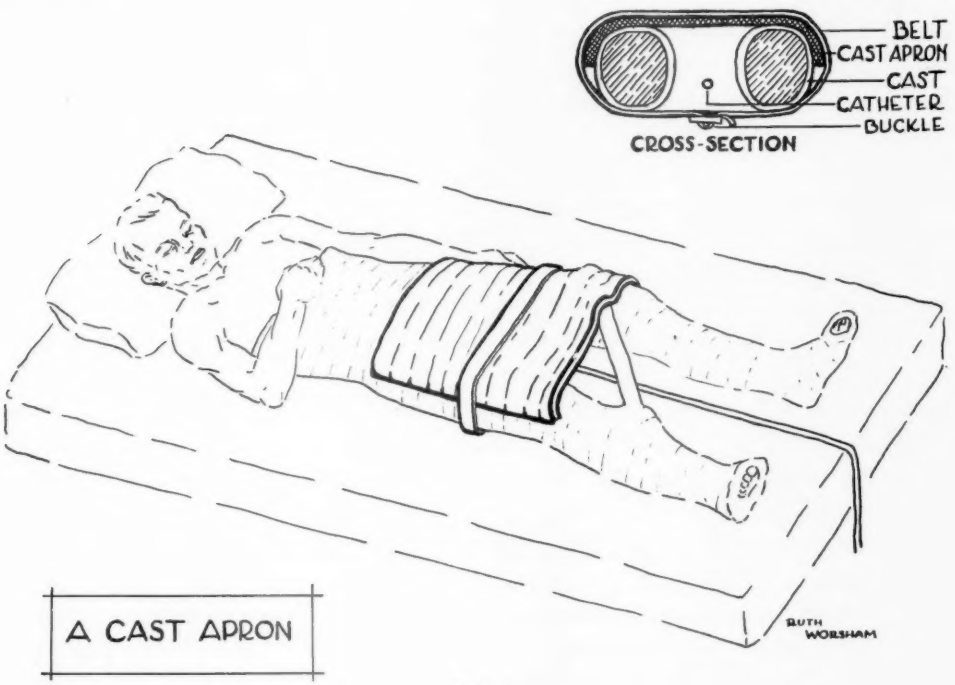

Fig. 1.

The plaster apron is made removable for reinsertion of catheters and for nursing care. The apron is easily constructed at the same time the spica is applied or subsequent to this. It consists of a few splints and rolls of plaster separated from the hip spica by sheet wadding. After the apron is trimmed and dried, a circular belt holds the apron in place. As further insurance against the patient's reaching his catheter it may be taped to the under side of the apron.

Received for publication, Sept. 19, 1951.

Case Reports

CONCOMITANT PYLORIC AND ESOPHAGEAL OBSTRUCTION DUE TO PEPTIC ULCER

CASE REPORT

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ROBERT E. MCALPINE, M.D., NORFOLK, VA.

PEPTIC ulcer of the esophagus was described first by Alders in 1839. There were occasional case reports after this, but these were incompletely described histologically. Quincke described three cases in 1879 which were confirmed histologically and from this report peptic ulcer of the esophagus became a clinical entity. Tileston reviewed the literature in 1906. He reported forty-four cases, three of which were his own. With the advent of fluoroscopy and esophagoscopy the diagnosis became more frequent, and Jackson, in 1928, reported eighty-eight cases of peptic ulcer found during the course of four thousand esophagoscopies for esophageal disease. Twenty-one were active ulcers and sixty-seven were scars from previous disease. The following year Friedenwald, Feldman, and Zinn added thirty-one cases, all of which were diagnosed by either fluoroscopy or esophagoscopy.

The reports of Tileston and Friedenwald, Feldman, and Zinn were very thorough and adequately discussed the symptomatology, pathology, incidence, etiology, diagnosis, and conservative treatment of the lesion.

The lesion is not common, but all authors agree that it is probably more common than is realized. In recent years esophagitis, ulceration, and chronic cicatrization of the lower end of the esophagus have been regarded as various stages of the same process. There has been no change in the etiological concept of the lesion since the report of Tileston, who said: "... in order that peptic ulcer should be formed, it is evidently necessary that the cardia should be insufficient, allowing regurgitation of the gastric juice into the esophagus. An important part is played in the etiology, therefore, by diseases associated with frequent vomiting, such as peritonitis, nephritis, chronic gastritis and especially ulcer of the stomach or duodenum. In the disease last mentioned, besides the vomiting, two factors are of importance: (1) ulcer of the cardia with organic insufficiency; (2) stenosis at the pylorus, with dilatation of the stomach, which may involve the cardiac orifice, with consequent relative insufficiency. The importance of the second factor is shown by the presence of stenosis of the pylorus or duodenum in eight of the cases with autopsy, or twenty-three per cent."

The case to be reported illustrates the association of duodenal and esophageal ulcer, and particularly the association between pyloric stenosis and esophageal ulcer.

Received for publication, Sept. 6, 1951.

CASE REPORT

J. L., a 64-year-old white man, was admitted to another hospital in Philadelphia on Sept. 20, 1949, with the chief complaint of epigastric pain and persistent vomiting of two weeks' duration. In addition, epigastric pain associated with episodes of vomiting had recurred during a period of 15 years. The family physician had treated him with powders. He had never had x-ray studies.

Gastrointestinal x-rays done Sept. 22, 1949, revealed a normal esophagus; the stomach was atonic and somewhat dilated; there was marked pylorospasm; after considerable delay enough barium passed through the pylorus to outline a rather markedly deformed bulb and a moderate sized ulcer crater in its center. At six hours there was considerable gastric retention. A diagnosis of partially obstructing duodenal ulcer was made.

He improved with medical treatment and a second gastrointestinal series of x-rays on Oct. 7, 1949, revealed no obstruction. However, there was more deformity of the duodenal bulb and a small residual crater was present. The esophagus was normal. The opinion was that he had an active duodenal ulcer, still present, with considerable fibrotic changes in the duodenal cap.

He was gastroscoped twice during his hospital stay and each time the esophagus was reported normal.

Laboratory studies, including gastric analyses, were within normal limits except for a moderate anemia which responded to blood transfusion.

He was discharged from this hospital on Oct. 25, 1949, with a diagnosis of duodenal ulcer. A program of ulcer treatment was instituted.

He was admitted to the Lankenau Hospital on Nov. 18, 1949. He had been relatively asymptomatic since discharge from the other hospital until four days prior to admission when he had developed persistent vomiting. After admission he was treated by parenteral fluids and allowed nothing by mouth. Vomiting ceased and his condition improved. He was placed on an ulcer diet. Four days later he had a recurrence of vomiting; this was regurgitation rather than vomiting. A Levine tube was supposedly passed into his stomach. An attempt to introduce a thin barium mixture through this tube was unsuccessful because the patient vomited and expelled the tube. The patient was operated upon Nov. 26, 1949. The preoperative diagnosis was pyloric obstruction secondary to duodenal ulcer.

Operation.—The abdomen was opened through an upper left rectus incision. Exploration revealed a marked inflammatory reaction about the pylorus and duodenum. Examination of the cardia and esophageal-cardiac junction revealed a stricture. The lumen of the stomach was explored through an anterior gastrotomy. The tube which had presumably been in the stomach could not be found. A small catheter could not be passed through the pylorus or through the cardia into the esophagus. An attempt was made to mobilize the lower end of the esophagus below the diaphragm. Both vagi were identified and divided. The esophagus could not be mobilized. It was obvious that there was a distinct stricture with marked thickening of the esophagus. The chest was then opened by extending the incision through the eighth intercostal space. The diaphragm was incised to the esophagus. Further exploration of the esophagus revealed marked thickening and adherence above the stricture site. The distal end of the esophagus was resected, the stomach closed and an esophagogastrostomy was performed above the diaphragm. An antecolic gastrojejunostomy was performed below the diaphragm.

The pathologist described an esophageal wall greatly thickened by mucosal inflammation, submucosal edema, and hypertrophy of the muscularis. The mucosa was ulcerated and its surface composed of granulation tissue with adherent fragments of necrotic tissue and fibrin. There were many dilated capillaries and a rather uniform exudate of lymphocytes and polymorphonuclear cells in the edematous submucosa. This extended into the circular muscle. The circular muscle fibers showed great hypertrophy in apparent compensation for associated stricture or other obstruction.

Diagnosis.—Chronic granulomatous esophagitis, with ulceration and interstitial hemorrhage.

Fig. 1.

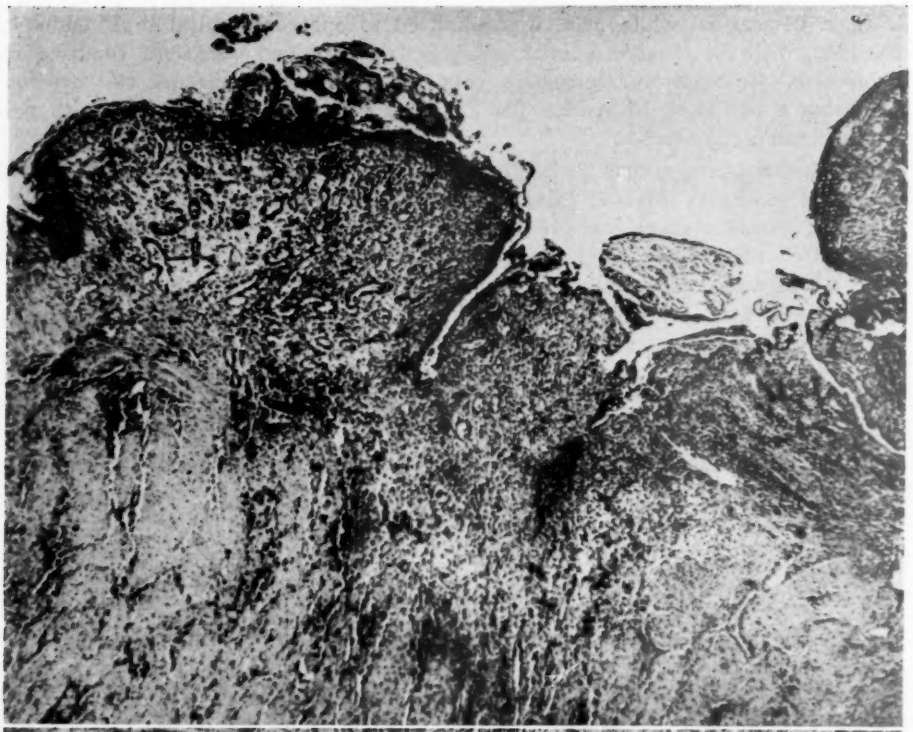

Fig. 2.

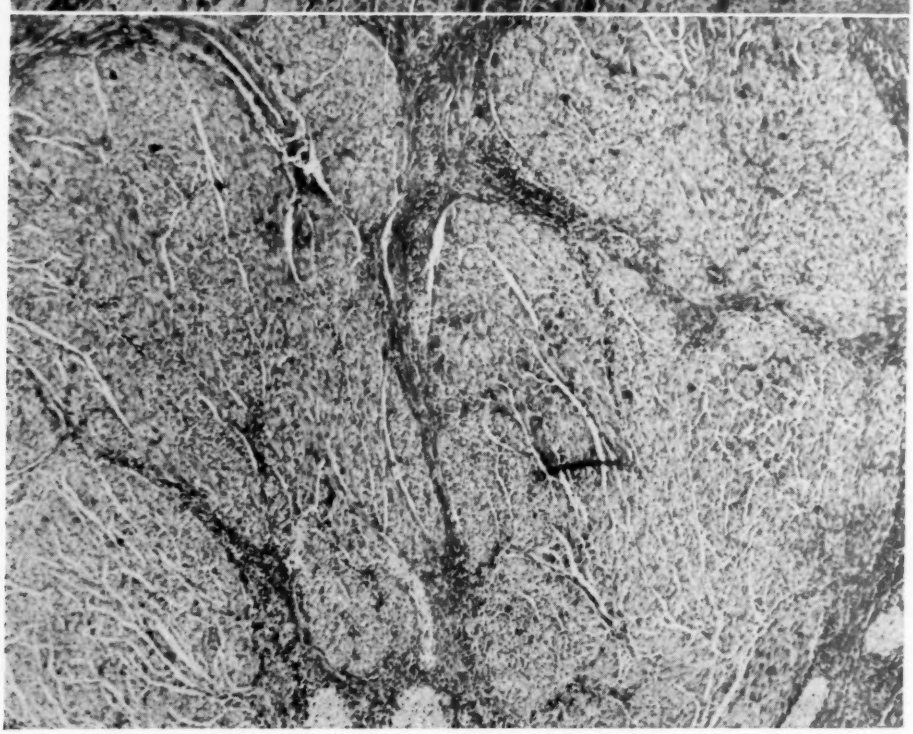

Fig. 1.—Ulceration of esophageal mucosa with chronic granulation tissue covering the ulcer bed.

Fig. 2.—Hypertrophy of the underlying muscularis and penetrating chronic inflammation of the interstitial tissue.

The patient made a relatively uneventful recovery and was discharged from the Lankenau Hospital on Dec. 19, 1949, with a diagnosis of duodenal ulcer and peptic ulcer of the distal esophagus with stricture formation.

Since discharge he has been on a modified ulcer diet, has gained weight and feels well; he has no difficulty in swallowing or drinking and has no substernal pain or discomfort. Follow-up gastrointestinal series reveal:

> Jan. 11, 1950: The esophagus at the level of the diaphragm just before it enters the stomach is somewhat narrow and constricted. The barium mixture readily passes this area, however. The enterostomy functions immediately and appears entirely normal. Some of the barium mixture leaves the stomach by way of the duodenum. The amount of barium mixture leaving by way of the duodenum is quite small in comparison to the amount leaving the stomach by way of the enterostomy.
>
> Nov. 24, 1950: This patient swallows thick and thin barium easily. The lower end of the esophagus for a distance of several inches is again seen to be somewhat narrow. The narrowing is *not* as pronounced as on the last examination (Jan. 11, 1950). There is a very slight constriction at the site of the anastomosis. This offers no obstruction whatsoever to the free passage of either thin or thick barium mixture. The lower end of the esophagus is a little irregular in outline when filled with barium mixture. This is probably of no significance.
>
> The enterostomy functions immediately and normally. A small amount of the barium mixture also leaves the stomach by way of the duodenum. The amount leaving by way of the duodenum is quite small in comparison to that leaving the stomach through the enterostomy.

Comment.—This case is unique in that an esophagus known to be normal on Oct. 7, 1949, progressed to complete stricture formation by Nov. 26, 1949, a period of fifty days. If we consider persistent vomiting the cause of his esophageal pathology, the stricture actually developed in twelve days. However, it is more logical to assume he had esophageal pathology prior to the last onset of vomiting. This is supported by the work of Friedenwald, Feldman, and Zinn, who, in 1928, reported an experimental study in dogs. They produced erosions of the esophagus mechanically and found they healed rapidly. When a ten per cent solution of hydrochloric acid was introduced into the esophagus through a tube four times daily, chronic ulceration developed only at the site of mechanical erosion. When the ulcers were allowed to heal and acid was not administered during the intervening period, further application of acid did not disturb the scar or produce any effect on the esophageal wall. On the basis of these experiments they concluded that ulcer of the esophagus was not caused by acid alone, but was certainly perpetuated by acid. They further state that this is evidenced by the fact that in many instances of the most aggravated types of pyloric stenosis this lesion is not produced.

This patient had esophageal trauma consisting of two gastroscopies and several intubations. Any of these procedures could produce an esophageal lesion, which in the presence of regurgitation and vomiting could progress to a granulomatous esophagitis.

Wangensteen, in recent experimental work using dogs and rats, has shown that the esophageal mucosa is far more susceptible to injury by acid-peptic digestive juice than gastric mucosa. From his experimental work and from clinical experience with six cases of esophageal stricture treated by subtotal

gastric resection, Wangensteen believes that esophagitis may be next in frequency to duodenal ulcer as a manifestation of the ulcer diathesis. He has advocated subtotal gastrectomy for esophageal ulcers of acid-peptic origin. An earlier

Fig. 3.

Fig. 4.

Fig. 3.—Preoperative roentgen film, Oct. 7, 1949.
Fig. 4.—Postoperative roentgen film, Jan. 11, 1950.

demonstration of this or similar procedures was cited by von Hacker and Lotheissen, in 1926. They reported an instance of pyloric stenosis associated with peptic ulcer of the esophagus in which healing of the esophageal lesion was achieved by means of gastroenterostomy. However, one of Wangensteen's cases

developed a peptic ulcer of the esophagus after having had a gastrojejunostomy for pyloric stenosis. This patient responded to subtotal gastrectomy, which further emphasizes the relationship of esophageal ulcer to gastric secretion.

In an elective case gastric resection is undoubtedly the treatment of choice. Although our experience is limited to this one case, gastrectomy was not feasible at the time of operation. The patient had a vagotomy and gastrojejunostomy which is our alternate treatment for ulcer of acid-peptic origin. Follow-up studies, to date, indicate this patient has been adequately treated for duodenal ulcer. We regard his esophageal lesion as a secondary or complicating factor and assume this will not recur unless he has recurrence of the duodenal ulcer causing interference with emptying of his stomach.

SUMMARY

A case of pyloric stenosis from duodenal ulcer and esophageal ulcer with stricture formation is presented. The patient has remained well following resection of the lower end of the esophagus, vagotomy, and gastroenterostomy.

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TYPHOID CHOLECYSTITIS

A Case Report

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WE WISH to present a case of typhoid disease complicated with acute cholecystitis and successfully treated by cholecystectomy. Since a review of the pertinent literature did not reveal a similar case, this condition was thought worthy of note.

REVIEW OF THE LITERATURE

In 1835, Huson[1] first indicated the presence of acute typhoid disease of the gall bladder when he reported a case of perforation of that viscus in a young woman who had typhoid fever. Later, in 1890, Gilbert and Girode[2] again focused attention on the relationship of cholecystitis to typhoid fever. By 1898, Keen[3] was able to collect thirty cases of acute cholecystitis during the course of typhoid fever. Rubenstein[4] illustrated the possibility of infection of hospital personnel with typhoid fever during the care of patients with cholecystitis. He concluded that typhoid involvement of the gall bladder should be considered in such cases.

It now seems established that the gall bladder and gastrointestinal tract act as foci for the typhoid bacillus. Forster[5] points out that while the normal gall bladder can readily destroy the typhoid organism, the diseased viscus is unable to do so. Zeligs[6] presented a case of typhoid cholecystitis improved by duodenal lavage. His case in the only one available in the literature which is similar to the case we are presenting.

No statistical data have been completed to determine the frequency of cholecystitis during the course of typhoid fever. Holscher[7] observed changes in the gall bladder in only 5 out of 2000 patients dying from typhoid fever. However, Mallory and Lawson[10] reported a distinguishing histologic picture for typhoid cholecystitis in 6.5 per cent of 400 routine gall bladder slides. These workers pointed out that although variations were present, they could recognize certain constant features in typhoid gall bladder disease. Thomas,[8] in 1907, collected 154 cases of cholecystitis during the course of typhoid fever in children. C. K. Chi[9] found only 4 cases of perforation of the gall bladder during typhoid fever between 1927 and 1939.

CASE HISTORY

Mrs. E. S. was a 62-year-old white woman admitted to the Buffalo General Hospital on May 28, 1947.* Admission complaints were chills, fever, nausea, and vomiting of six days' duration. The patient stated that except for occasional anorexia and weakness

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*To the service of Dr. Clayton Greene.

she felt well until May 22, at which time she developed severe chills and fever. Inventory of the systems was noncontributory. The patient denied contact with any known typhoid carrier, but did admit drinking water from a local unpurified source.

Physical examination revealed an elderly, gray-haired woman who was acutely ill. The skin was dry and a moderate pallor was evident. No evidence of jaundice existed. The nose and throat were essentially within normal limits. Although a tachycardia was present on admission, the heart was normal to clinical examination. No findings were noted on examination of the pulmonary fields. The abdomen was soft and without evidence of previous surgery. There existed definite tenderness over the right upper quadrant but no mass was palpable.

The red cell count was 4,000,000 cells per cubic millimeter of blood and the hemoglobin was reported at 11.5 Gm. The white cell count was 6,300 cells per cubic millimeter of blood with a normal differential distribution. Urinalysis revealed no glucose and a one plus albumin. On microscopic examination, the urine was found to contain 40 to 50 red cells and many sulfa crystals. The van den Bergh test was normal at the time of admission, but the cephalin flocculation test was positive with a reading of four plus. An admission blood culture was positive and identified as *Eberthella typhosa*. Agglutination reaction on May 28 revealed the H antigen to be 1/160 while the O antigen showed a titer of 1/1280.

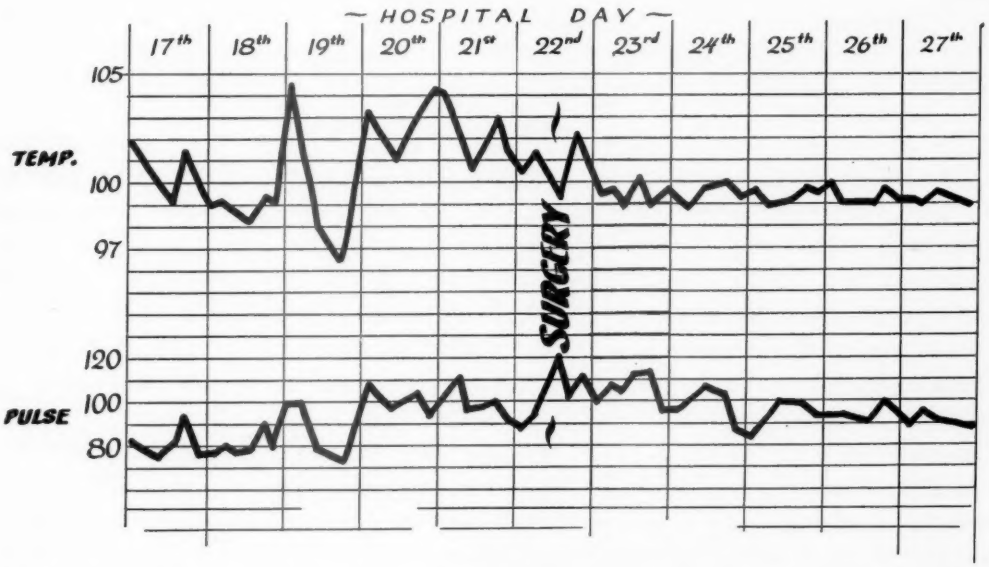

Fig. 1.—Temperature record showing preoperative and postoperative course. Note change in temperature following surgery and presence of bradycardia previous to surgery.

A diagnosis of typhoid fever was established and conservative therapy instigated. Penicillin, supportive measures, and bed rest constituted the regimen. During this period the temperature persisted at 104 to 105° F. rectally and the average pulse rate was 94 beats per minute. The patient continued to have nausea and vomiting with persistence of the right upper quadrant pain. The hospital course was septic in type with a change in the blood picture to 3,000,000 red cells per cubic millimeter of blood and 7.8 Gm. of hemoglobin. The white cell count remained at 6,000 cells per cubic millimeter of blood. By this time the stool and vomitus cultures were positive for *E. typhosa*.

Streptomycin was suggested on the fourth hospital day in place of the penicillin. The patient received 8.5 Gm. of streptomycin without apparent clinical improvement. Because of the persistent tenderness in the right upper quadrant, surgical consultation was requested. A diagnosis of acute cholecystitis was made and immediate surgical intervention recommended.

On June 18, the patient was operated upon and a large, distended, thickened, and acutely inflamed gall bladder was encountered. There was a stone impacted in the cystic duct. The common duct was inspected and appeared normal except for surrounding edema. Cholecystectomy was readily accomplished and a drain was placed in Morison's pouch. The abdominal wall was closed in layers.

The report of the pathology department indicated an acute, hemorrhagic cholecystitis. The viscus wall measured 1 to 2 cm. in thickness and the mucosal surface was hemorrhagic and ulcerated. In one area there were several pea-sized abscesses within the serosa. There was microscopic evidence of ulceration and necrosis of the mucosa.

The postoperative course of this patient was extremely interesting. The temperature elevation subsided within twelve hours after surgery. (Fig. 1.) The pulse rate remained at 90 beats per minute but became more stable within 24 hours. On the first postoperative day the patient improved considerably and continued to do so throughout her convalescence. The drain was easily removed on the seventh postoperative day and the incision healed per primam. Following the cholecystectomy the patient experienced no complications or recurrence of her typhoid state. Her temperature and pulse remained within normal limits during hospitalization and were normal at time of discharge. The patient was discharged from the hospital on the thirty-fourth postoperative day.

Cultures of the stone and gall bladder taken at the time of surgery were positive for *E. typhosa.* In the laboratory the crushed stones were positive on culture.

Postoperative stool and urine cultures were negative and remained so. Follow-up examinations carried out by the Health Department of the State of New York on stool specimens were negative on July 30, August 5, and August 10 of 1947.

DISCUSSION

It is interesting to note the dramatic improvement and apparent cure of the case presented here. Clinically, the patient presented all the essential symptoms, signs, and laboratory evidence to establish a diagnosis of acute typhoid fever. As a complication of this systemic disease there developed evidence of acute cholecystitis. The unusual feature of this case is the prompt clinical arrest of the systemic disease by cholecystectomy. To speculate on the morbid physiopathology present at the time of surgery is justifiable only in the light of our present limited knowledge. From the postoperative course it appears that the infection of *E. typhosa* was limited to the gall bladder and that the removal of this acutely diseased viscus resulted in a clinical cure of the primary, systemic disease. This is obviously an application of the long-understood principle of elimination of foci of infection. It is revealing that such should apply so completely to a disease of this nature.

SUMMARY

1. The available literature concerning surgery of the gall bladder and associated typhoid fever is reviewed.

2. A case of typhoid fever associated with acute cholecystitis is reported, with an apparent cure of the typhoid disease by cholecystectomy.

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PERFORATED GASTRIC ULCER IN ACUTE DIAPHRAGMATIC HERNIA

Case Report

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AN UNUSUAL manifestation of blunt trauma to the chest was encountered in a recent patient sustaining a crushing injury of the thorax and abdomen. This patient presented a traumatic diaphragmatic hernia with incarceration of the anterior surface of the fundus of the stomach above the left diaphragm. Perforation of an acute peptic ulcer in the incarcerated stomach occurred on the fourth day after injury, resulting in a thoracogastric fistula and early empyema.

CASE REPORT

W. E. L. (Baptist Hospital No. 5365), when seen two hours after an auto accident, was in profound shock. Respirations were shallow and rapid; there was evidence of faint cyanosis. Antishock therapy was immediately instituted, but the response to these measures was noticeably slow although 2,500 c.c. of blood were given promptly. Physical examination revealed bilateral rib fractures with no discernible evidence of paradoxical respiration. The abdomen was mildly distended but presented little tenderness. There was gross hematuria, apparently from renal contusion.

Twelve hours after injury, the patient presented a typical "wet lung" with dusky cyanosis, rapid, shallow and bubbling respirations, and ineffectual cough. This was combated by tracheobronchial catheter aspiration every four to five hours. Intercostal block with novocaine was deferred as chest pain per se was not a major factor. A portable chest film at this time revealed elevation of the left leaf of the diaphragm suggesting eventration or diaphragmatic hernia. For this reason no thoracentesis was done, although there was clinical evidence of a left pleural effusion.

During the next four days the patient presented slight improvement with less hematuria and resumption of normal bowel sounds. Meticulous tracheobronchial toilet was necessary to prevent clinical cyanosis. Studies three days after admission revealed a normal cystogram although there was a fracture of the pubis. Chest film (Fig. 1) disclosed herniation of much of the stomach into the left thorax.

Four and one-half days after injury the patient presented sudden, severe pain in the lower left chest associated with drenching perspiration. There was no change in the blood pressure or pulse rate. It was necessary to increase the sedation to allay this pain. The temperature, which had been normal, increased to 100.6° F. There was no evidence of intestinal obstruction for the abdomen was flat and the patient had a spontaneous bowel movement. The possibility of strangulation of the stomach within the diaphragmatic hernia was considered, but seemed unlikely as the fluid aspirated from the stomach by means of a Levine tube was not blood tinged. Twenty-four hours after development of the severe pain in the lower left thorax, there was clinical and radiologic evidence of increasing shift of the mediastinum to the right with more fluid within the left chest (Fig. 2). Exploratory thoracotomy was therefore advised in spite of the patient's precarious condition.

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Operation.—Under endotracheal anesthesia the left thorax was opened through the bed of the resected eighth rib. The left lung was collapsed about 50 per cent and the pleural space filled with approximately 500 c.c. of thin, greenish yellow fluid containing small flakes of fibrin. The left diaphragm presented an irregular laceration adjacent to, but not connected with, the esophageal hiatus. Most of the fundus of the stomach protruded through this abnormal opening. The entire diaphragm and herniated stomach were covered with a sheet of fibrin about 3 mm. in thickness. Phrenic palsy was noted. A typical perforated peptic ulcer, measuring about 4 mm. in diameter, was found just above the greater curvature of the incarcerated stomach (Fig. 3). This was easily closed with a double purse string suture. The incarcerated stomach was reddened and edematous but showed no evidence of impaired circulation. The diaphragm was opened radially and the stomach reduced. A large subcapsular hematoma of the spleen necessitating splenectomy was encountered. The rent in the diaphragm was closed with some difficulty and the lung easily decorticated, allowing full expansion. The chest was closed after introduction of antibiotics and the insertion of intercostal catheters.

Fig. 1.

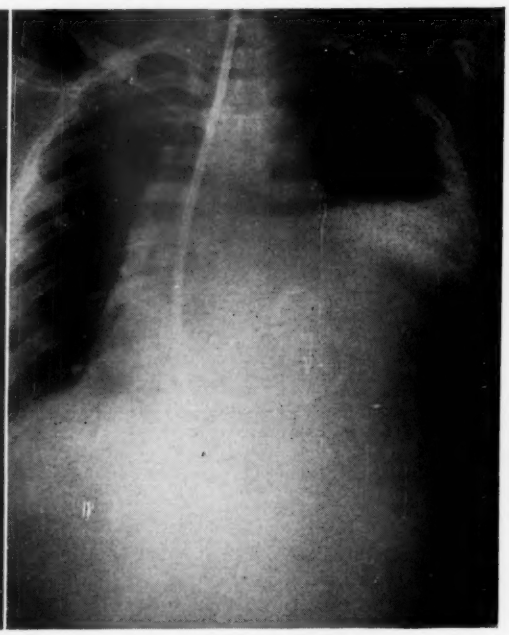

Fig. 2.

Fig. 1.—Chest film showing herniation of the fundus of the stomach into the left chest.
Fig. 2.—Preoperative chest film showing increasing mediastinal shift with more marked pleural effusion. The tip of the Levine tube is coiled in the incarcerated stomach.

Postoperatively the patient did quite poorly presenting a temperature of 105° to 107° F. despite strenuous antipyretic measures. He died 18 hours after surgery.

Autopsy.—The essential post-mortem findings were: (1) bilateral rib fractures, (2) patchy atelectasis of left lung and right lower lobe, thick mucopurulent tracheobronchial exudate, (3) sutured traumatic rupture of left diaphragm, (4) postoperative repair of gastric ulcer, (5) multiple superficial gastric ulcers, (6) left thoracic empyema (early).

The anterior surface of the proximal half of the stomach was coated with thick grayish brown exudate. A small closed perforated ulcer near the greater curvature and 90 mm. from the esophagus was evident. Marked superficial ulceration of the mucosa of the fundic portion of the stomach was seen. There were innumerable tiny ulcers (Fig. 4) involving primarily the mucosa, but occasionally extending into the submucosa and even into the muscularis.

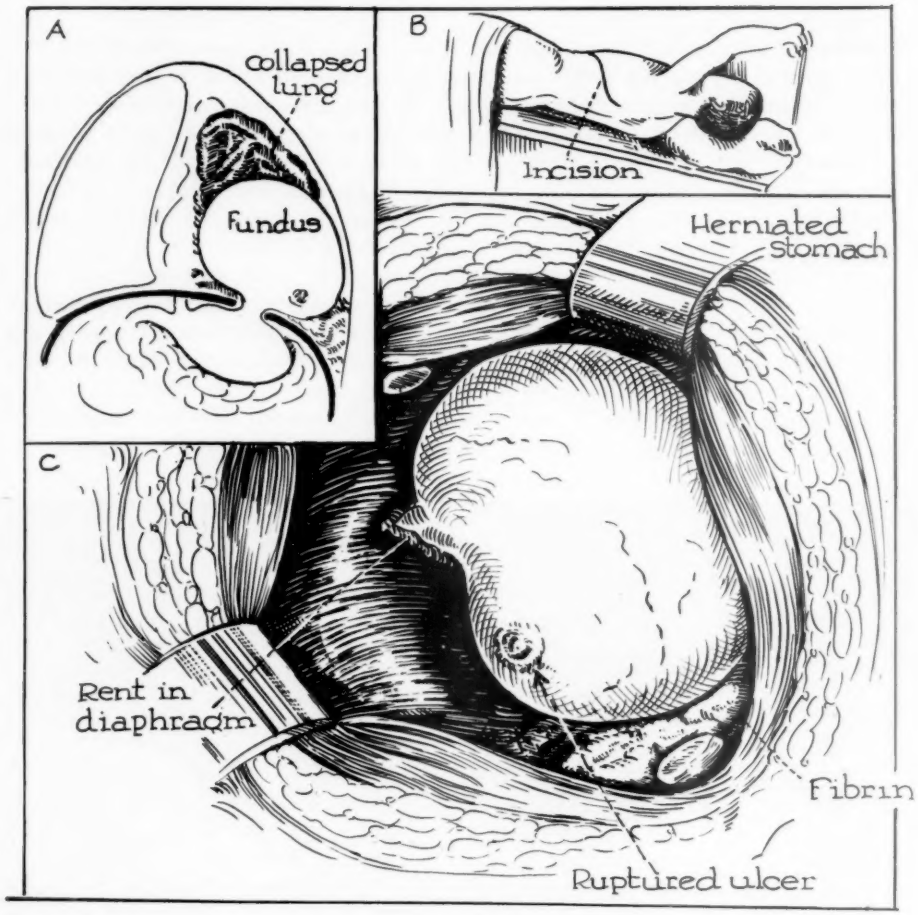

Fig. 3.—Diagram showing the perforated gastric ulcer in the incarcerated diaphragmatic hernia.

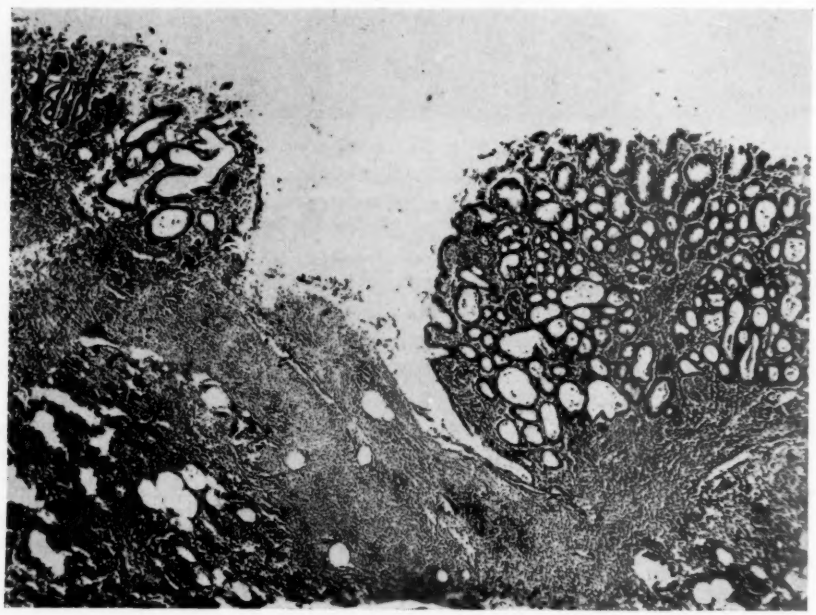

Fig. 4.—Photomicrograph showing one of the innumerable acute ulcers of the gastric mucosa.

DISCUSSION

This case is presented for the following reasons:

1. An unusual complication if an acutely incarcerated diaphragmatic hernia is described.

2. The development and perforation of such an acute peptic ulcer may shed some light on the genesis of thoracogastric fistulas in acute chest injury. In the past these fistulas have been uniformly ascribed to the trauma of thoracentesis. There is no question that the defect in the stomach would have been blamed on an inadvertent needle puncture in this case had a thoracentesis been done, for the defect was small and not unlike that expected from such penetrating injury. As there had been no thoracentesis, this was obviously not an etiologic factor.

It is not too surprising to have peptic ulceration, even with perforation, develop rapidly in traumatic diaphragmatic hernias. If the factors favoring the development of acute peptic ulceration when the fundus of the stomach is incarcerated in a diaphragmatic hernia are considered, the possibility of such ulceration is at once obvious. Here, the fundic portion of the stomach (containing the glands secreting both acid and pepsin) was so trapped that there was accumulation of acid-pepsin with an opportunity for prolonged action on traumatized gastric mucosa. The process of autodigestion was further enhanced by the relative starvation which usually follows such severe injuries, and an increase in histamine secondary to trauma and prolonged anoxia.

3. The onset of sudden severe chest pain in a patient with stomach entrapped in a traumatic diaphragmatic hernia should at once suggest the possibility of a perforated peptic ulcer with thoracogastric fistula. Had this fact been more fully appreciated, operation would have been performed twenty-four hours earlier and the result might have been different.

SUMMARY

A case of traumatic diaphragmatic hernia, which may be enlightening on the pathogenesis of thoracogastric fistula, is presented.

RADIATION INJURY TO THE SMALL INTESTINE

A Report of One Case of Massive Hemorrhage and One of Perforation Following Therapy for Carcinoma of the Cervix

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RADIATION injury to adjacent structures during treatment for carcinoma of the cervix or of the uterus has always been a source of concern to the physician.[1] The rectum, being in closest proximity, is the structure most frequently damaged[2]; however, injuries to the bladder, the ureters,[3] and the small intestine[4] have also been described.

When the small intestine is damaged by radiation, intestinal obstruction is the usual complication which brings the patient back under treatment. Instances of massive hemorrhage or of perforation of ulcerations in the small intestine as the result of radiation injury are not common. The occurrence of one of each of these complications recently at the Duke Hospital has prompted this report.

Immediate effects of irradiation on the intestine occur frequently.[5] They usually begin during the course of treatment and rarely last longer than two or three weeks after the irradiation is stopped. The usual symptoms are nausea, diarrhea, or cramps; however, severe bloody diarrhea and marked constitutional symptoms may develop. The pathologic lesion[6] is one of edema and hyperemia of the intestinal mucosa. In severe reactions multiple ulcerations and even gangrene in the bowel have been reported.

The delayed manifestation of irradiation injury in the small intestine is essentially an ulcerative process or the sequelae of ulceration. Clinical symptoms usually appear between 6 and 12 months after injury; however, in some cases symptoms may not occur for many years. Jones[7] and Frank and Pohle[8] reported cases in which symptoms did not develop for eight years, and in our first case, twelve and a half years had elapsed before intestinal lesions caused trouble. The ulcers may be single or multiple. They may be superficial or deep. Penetrating ulcers may perforate into the peritoneal cavity (Case 2) or into surrounding viscera with the formation of a fistula. Massive hemorrhages are not common, but were the cause of admission of our first case. Healing of the deeper ulcerations often results in a cicatrix which causes intestinal obstruction.

Our first patient (Case 1) had massive hemorrhages from three ulcerating stenosing lesions in the terminal ileum. She also had a stenosing ulcerating lesion in the rectosigmoid. She had had intracervical and intravaginal radium therapy and x-ray treatments over sacral and abdominal ports twelve and one-half years previously. Operation was necessary because of continuous bleeding from the bowel of two weeks' duration. A 19 cm. segment of terminal ileum

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containing three bleeding ulcers and an 11 cm. segment of rectosigmoid were resected and primary anastomosis done at each site. Her convalescence thereafter was uneventful and she has had no bleeding from the bowel since.

Our second patient (Case 2) had a walled-off perforation in a necrotic segment of terminal ileum six months following x-ray treatment and intracervical and intravaginal radium in the cervical stump. At operation it was necessary to resect the necrotic portion of small intestine. An end-to-end anastomosis was done in the presence of an almost complete intestinal obstruction and gross soiling. She developed a fecal fistula postoperatively which closed spontaneously.

CASE 1 (Duke 98881).—A 67-year-old white woman was admitted Dec. 5, 1950, because of repeated large bloody stools during the preceding week. Thirteen and a half years previously a diagnosis of carcinoma of the cervix had been made elsewhere and she was given five x-ray treatments of unknown amount. She was first seen in this hospital thirteen years ago at which time she received an additional 4,400 mg. hours of intracervical and intravaginal radium and 4,500 r. x-ray therapy over four sacral and four suprapubic ports. She had some nausea during irradiation treatment and had minor symptoms of proctitis six months later. Thereafter she was seen frequently by the gynecologists for check-up examinations, by the internists for arthritis, and by the psychiatrists because of a depressive state. There was never any evidence of recurrence of her carcinoma and in 1947 when we removed her gall bladder because it was full of stones and causing pain, the uterus was atrophic and no carcinoma in the pelvis or elsewhere was detected. Her appendix was also removed at this time; however, the small intestine was not inspected.

There were no bowel symptoms of consequence until May, 1950, twelve and one-half years after irradiation therapy, when she passed a large stool of brown and red clotted blood. This was repeated on the following two days. When she was admitted to the Duke Hospital on the fourth day of her bleeding episode her hemoglobin was only 34 per cent. She was given 1,500 c.c. of blood by vein, her bleeding stopped spontaneously and after eight days in the hospital she was discharged with a hemoglobin of 8.4 Gm. or 54 per cent. Proctoscopy at this time showed a rather smooth stenosis of the rectosigmoid at a depth of 14 cm. from the sphincters. The bowel at this depth would just admit a small cotton applicator. Within the stenosed area the lower margin of a shallow ulcer with a grayish white avascular base could be seen. There was no evidence of old blood or fresh bleeding about the ulcer. A barium enema showed the bowel to be narrowed in this area. There were numerous diverticula along the transverse and descending colon.

Thereafter she passed no more blood per rectum for six months, when on Dec. 1, 1950, she again began having one to two large bowel movements of dark blood daily, and was hospitalized elsewhere and transfused. Bleeding continued and she was readmitted to the Duke Hospital on Dec. 5, 1950. Daily, 500 c.c. transfusions were given: however, she continued to pass large bloody stools daily and after one week her hemoglobin had not risen above the level of 51 per cent on admission. Proctoscopy showed the same stenosis with avascular ulcer at a depth of 14 cm. Barium enema showed the same zone of narrowing in the rectosigmoid. X-ray studies of the barium-filled small intestine showed no obstruction; however, there was some mucosal distortion and possible ulceration in the ileum.

In the belief that she was bleeding from an area of radiation ulceration at the rectosigmoid we operated upon her Dec. 15, 1950, with the intention of resecting the involved segment of colon. At operation, when the small bowel was inspected, it was seen that she had three stenosing thickened areas in the terminal ileum about two feet above the ileocecal valve. These three lesions were about 8 or 10 cm. apart. They appeared to be annular scars in the bowel which had constricted the bowel to the point where there seemed to be no lumen left, although there was no evidence of intestinal obstruction. Each was about 1 cm. in length. The remainder of the entire small intestine was negative. When we examined the colon we found a similar lesion in the rectosigmoid junction where at about the level of the uterosacral ligament there was a stenosed thickened area in the bowel with some

thickening in the mesentery adjacent to the bowel. The small bowel lesion was approached first and was resected between clamps and an end-to-end anastomosis done. The rectosigmoid was then mobilized from the hollow of the sacrum as far as the coccyx, after peritoneal flaps along each side of the mesentery of the bowel had been fashioned. The lesion, when mobilized, could be brought up to within about 8 cm. of the abdominal wall. It felt like an annular thickened cicatrix and there was also some thickening in the mesentery. This mesenteric thickness encircled the inferior mesenteric artery and in order to free the lesion completely it was necessary to divide the inferior mesenteric artery above and below the lesion. A 12 cm. segment of terminal sigmoid and rectosigmoid was then resected and an end-to-end anastomosis made.

When the resected small intestine was opened it was seen that the bowel was thickened and stenosed and contained a shallow ulcer about 0.5 cm. in width which entirely encircled the bowel at each one of the three involved areas. Each of the ulcers had old blood in its base. The lesion in the colon contained a similar constricting cicatrix which just admitted the tip of the little finger. It was about 2 cm. in length and contained one shallow 1.2 by 0.2 cm. avascular ulcer. Microscopic studies of all four lesions showed nonspecific ulceration with scarring.

She had a smooth postoperative convalescence and was discharged on her thirteenth postoperative day.

CASE 2 (Duke C 86517).—A 43-year-old Negro woman was admitted Jan. 15, 1951, five months following radiation therapy for squamous-cell carcinoma of the cervical stump, stage 2 to 3, for evaluation of a pelvic mass.

Three years previously, in 1948, she had had a supravaginal hysterectomy elsewhere for prolonged and profuse uterine bleeding. In April, 1950, following a six months' history of bloody vaginal discharge, a biopsy of the cervix was done and reported as squamous-cell carcinoma. In May of 1950 she was referred to this hospital and started on a series of x-ray therapy, being given a total of 16,100 roentgen units, of which 3,500 roentgen units were administered through a transvaginal cone. This therapy was completed in June of 1950. On July 31, 1950, she was readmitted and given 3,600 mg. hours of intracervical radiation with radium and 1,450 mg. hours of intravaginal radium.

On readmission to the hospital on Jan. 15, 1951, she complained of urinary frequency and dysuria, the passage of bright red blood from the rectum on defecation, and almost constant lower abdominal and back pain. On examination her temperature, pulse, and respiration were normal. She appeared chronically ill. The abdomen was flat and showed tenderness to pressure above the symphysis pubis. On vaginal examination the cervix was found to be small, fibrous, and fixed. There was a large, firm, slightly tender mass felt in the pelvis behind the bladder which rose about 10 cm. above the symphysis pubis on the right and 8 cm. on the left. There was bilateral parametrial induration. The hemoglobin was 11 Gm. The white blood count was 9,150. The urine was essentially normal.

She was placed on 300,000 units of penicillin daily and during the next two weeks the symptoms gradually subsided and the pelvic mass decreased in size. The temperature had almost daily rises to 100° F. On January 28 she began having peristaltic pain and a plain x-ray of her abdomen showed dilated loops of small bowel in the upper abdomen. The temperature was not elevated. After 48 hours of continuous siphon drainage of the stomach with a Levine tube, her condition was not improved and she was operated upon.

At operation on Jan. 30, 1951, the abdomen was opened through the old lower midline incision. The peritoneal cavity contained about 1,000 c.c. of straw-colored fluid. Small intestinal loops were dilated. The small bowel was matted together and adherent in the pelvis where a perforation was found in a 2 cm. necrotic segment of ileum. This perforation had been sealed off by several loops of bowel which were matted together but was opened during the operative procedure and soiling of the peritoneal cavity occurred from small bowel contents and from pus. It was necessary to resect a 10 cm. segment of small intestine including the necrotic portion of the bowel, and an end-to-end anastomosis was done.

She had a stormy postoperative course, developed a fecal fistula, and left the hospital on her thirty-second postoperative day. The fecal fistula subsequently closed.

DISCUSSION

The incidence of injury to the small intestine during radiation therapy for carcinoma of the cervix is not high. Wiley and Sugarbaker[4] found it in 9 of 600 cases and Waterman and Tracy[9] in 3 of 489 cases treated for carcinoma of the cervix or uterus.

Some observers believe that radium introduced into the cervix is more frequently the cause of radiation injury to the bowel than x-ray therapy. It has also been emphasized that the intestine is more vulnerable to injury if a supravaginal hysterectomy has been done previously. Wiley and Sugarbaker noted that all of their patients who suffered radiation injury to the bowel were quite thin.

The radiation injury to the small intestine is essentially an ulcerating process which may bleed, perforate, or cause obstruction to the intestinal tract when the ulcers stenose during the process of healing.

The treatment of the sequelae of radiation ulcerations in the small intestine is essentially the same as the treatment of any other ulcerating or obstructing process in the bowel. Resection of the damaged segment of intestine with primary anastomosis is usually the ideal treatment. In the case of localized perforations complicated by intestinal obstruction, as in our Case 2, Wiley and Sugarbaker advise that a sidetracking operation rather than a primary resection be done.

CONCLUSION

It is important that the surgeon recognize that radiation therapy over the abdomen or through the vagina may cause intestinal ulcerations which may bleed, perforate, or cause intestinal obstruction. Complications may occur as late as twelve years after the radiation treatment. If any of these complications develop in a patient previously irradiated for carcinoma, hasty judgment that the carcinoma has recurred and is the cause of trouble should be withheld and the possibility of radiation injury considered until definite evidence of recurrence is proved.

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BRACHIAL PLEXUS AND SUBCLAVIAN ARTERY EMBARRASSMENT CAUSED BY HEMORRHAGE INTO THE SUPRACLAVICULAR FOSSA

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THE syndrome of lower cord (brachial plexus) and subclavian atery compression by the anterior scalene muscle, cervical rib, and anomalous first rib, and variations in relationship of the shoulder girdle to the dome of the thorax are well recognized.[1, 3, 4]

Similarly, the relationship of these structures to the fascial planes of the neck and the distribution of these planes with reference to each other have been worked out in detail and are well known.[2]

It is felt that the following case presents an interesting and unusual result of the influence of one set of anatomic relationships upon the other.

CASE REPORT

A 23-year-old white woman was first seen six weeks after having been delivered of her first pregnancy. On the first post-partum day the patient had crawled to the foot of her bed, leaning over the end to crank up the head. She felt a minimal transient stabbing discomfort in the right supraclavicular fossa with this effort. Within twenty minutes severe aching pain developed in the supraclavicular region radiating into the neck and face and right arm in the distribution of the ulnar and median nerves. The pain became progressively more severe and intractable and was unrelieved by morphine. This persisted, not responding to immobilization, elevation, heat, or narcotics.

When seen six weeks after the onset of the discomfort, the head was held tilted to the right and forward. Neck length was exaggerated because of slope-shoulder habitus. There was suggestive fullness and extreme tenderness of the right supraclavicular fossa and any active or passive movement of the arm accentuated the pain.

The right arm was held in complete adduction, the shoulder thrust forward and the forearm flexed across the chest. The right elbow was held cupped in the palm of the left hand, the right hand was cold, the radial pulse was present but markedly diminished when compared to the left. There was hypesthesia in the distribution of the ulnar sensory supply up to the elbow and definite weakness of grip in the right hand.

A diagnosis of acute anterior scalene muscle spasm seemed feasible since no other explanation was apparent clinically or radiologically (Fig. 1).

The supraclavicular fossa was entered for the purpose of performing anterior scalenotomy. When the deep cervical fascia was incised, approximately four ounces of black, partially organized clotted blood were extruded. No source for the hemorrhage was discovered. The wound was thoroughly débrided of clot. The subclavian artery appeared to be in partial spasm without full pulsation. Following anterior scalenotomy, it was seen to resume normal diameter and to pulsate freely. Immediately postoperatively the patient was symptom free and comfortable for the first time in six weeks.

DISCUSSION

Explanation of the development and persistence of symptoms and signs is apparent when the relationship of the neurovascular structures to the muscle and fascial planes of the neck in the supraclavicular fossa is considered (Fig. 2).

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Unlike the subclavian artery, the vein is intimately bound by the tough cervical fascia as it courses posterior to the clavicle in intimate relationship to the subclavian muscle. Therefore, any one of its minor tributaries traversing the tough deep cervical fascia could be torn if subjected to forces of distention and torsion such as would be placed upon them by the awkward and unusual effort which the patient undertook in adjusting her bed.

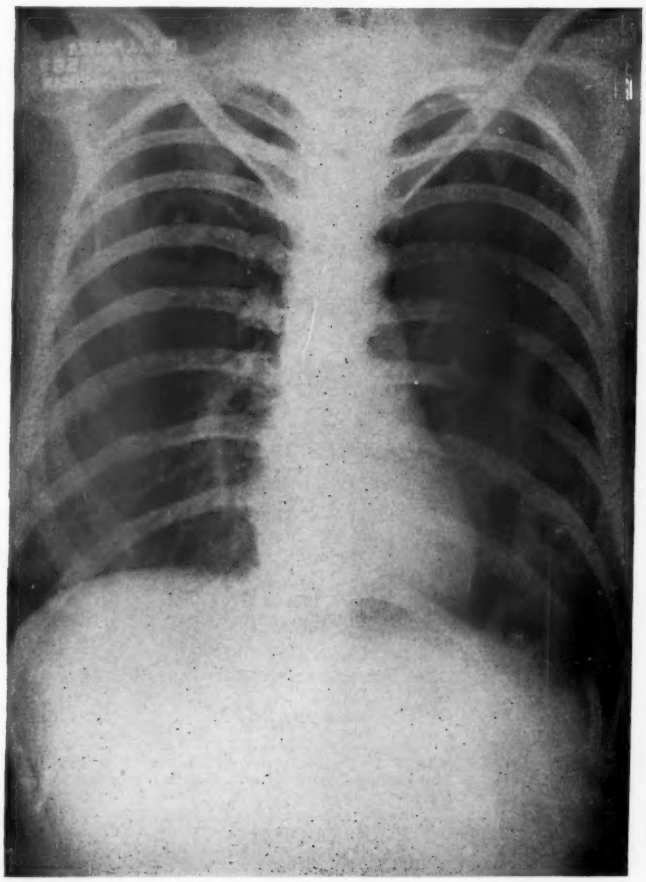

Fig. 1.—Posteroanterior stereogram of the chest showing suggestive cloudy increase in density over the right apex.

Venous bleeding into the space bounded by the deep cervical fascia and the prevertebral fascia covering the scalene muscles would be confined under pressure and therefore self-limited by tamponade after a brief period. However, in a situation already favoring compression of the plexus and subclavian artery, as in this slope-shouldered individual such a readjustment and embarrassment of available potential space produces marked symptoms reflecting the structures involved.

It is possible that in an individual lacking the anatomical predisposition favoring compression of the plexus and artery by the anterior scalene muscle, only transient local symptomatology might have occurred.

SUMMARY

An unusual case of compression of the brachial plexus and subclavian artery (anterior scalene syndrome) due to hemorrhage from one of the venous tributaries to the subclavian vein is presented.

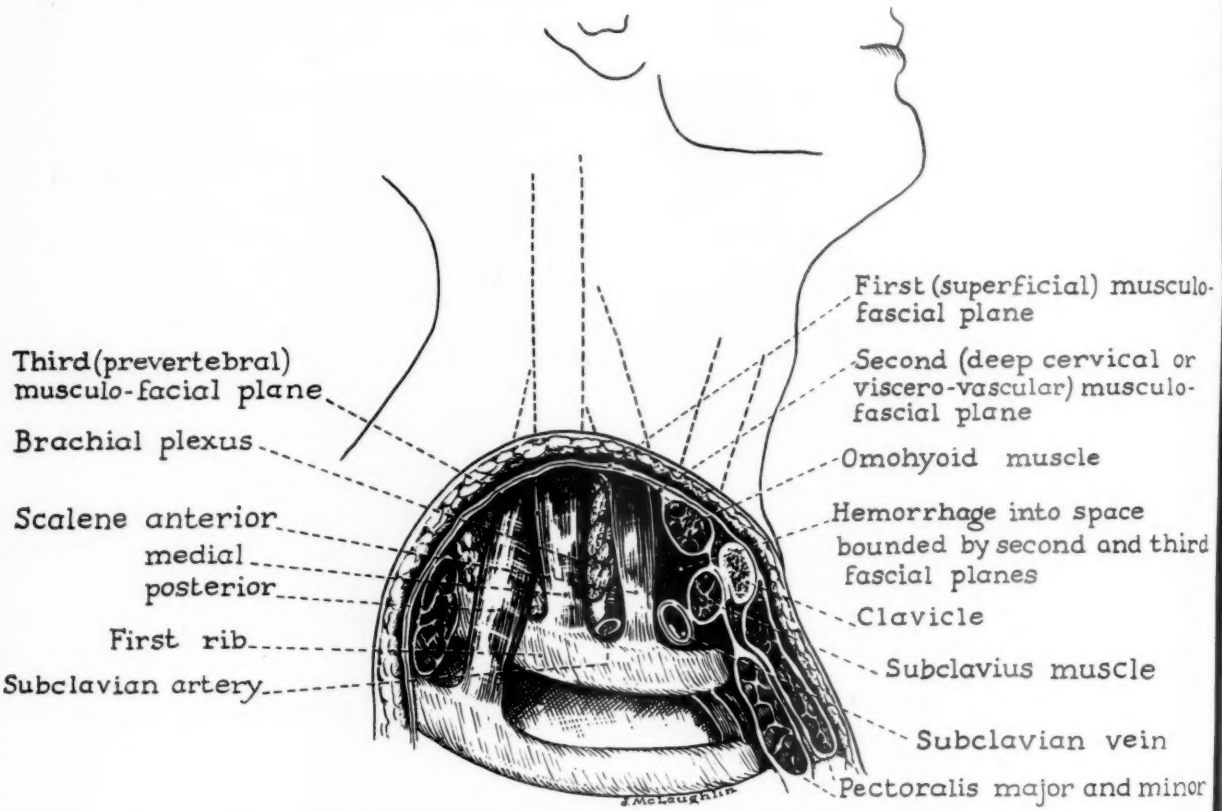

Fig. 2.—Diagrammatic reconstruction of the relationship of the subclavian artery and brachial plexus to the second and third fascial planes.

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PERICARDIAL CELOMIC CYST

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THE clinicopathologic entity, pericardial celomic cyst, became a contemporary problem with Pickhardt's description of the first successful surgical removal of such a cyst in 1934.[1] Since that time, the removal of 61 additional such cysts have been reported in the English literature. With the accumulation of case reports certain impressions made from the observation of one or two cases appear erroneous. A careful review of the literature and 11 proved pericardial celomic cysts removed surgically at Fitzsimons Army Hospital between January, 1945, and July, 1951, are being reported.[1-35] Four are recorded in detail.

The most widely accepted and workable explanation of the embryological basis for the development of these cysts is that of Lambert which is based on Wilhelm His' description of the development of the pericardium.[3, 27] The lack of agreement upon the embryological basis for the development of these cysts has given rise to the multiplicity of terms by which they are known, including: pleuro-diaphragmatic cyst, simple cyst of the mediastinum, spring-water cyst, mesothelial mediastinal cyst, and pericardial celomic cyst.[1, 3, 4, 6, 7] The latter term seems to be the most acceptable. Table I summarizes the English literature of the case reports which appear to fulfill the following criteria: first, the cyst wall is thin, transparent, and covered by mediastinal pleura; second, the cyst is filled with clear fluid; third, the cyst is lined by a single layer of mesothelial type cells.

The literature contains many statements which infer that pericardial celomic cysts are innocuous and rarely produce symptoms.[9, 10, 24] In our 11 patients, 6 had symptoms referable to mediastinal pressure, interference with respiration, or cardiac action which resulted in a roentgenogram of the chest being made. Drash and Hyer found symptoms present in 76 per cent of 21 cases reviewed.[5] In Lillie's report of 12 patients, 7 had symptoms.[11] It is recognized that there is a functional as well as an organic component in the symptom complex. It is not uncommon for symptoms to appear in asymptomatic individuals when they are informed of the presence of the cyst. Likewise, psychogenic exacerbation of symptoms often occurs in the already symptomatic individual. The symptom most constantly noted is pain, which is usually mild and precordial. Pain in one shoulder is common. Epigastric discomfort and pain radiating around the costal cage is frequent. There may be exertional dyspnea, nonproductive cough, and hemoptysis. Difficulty in swallowing, palpitation, tachycardia, and, as in one of our cases, marked paroxysmal tachycardia may be noted. Symptoms improve or abate following removal of the cyst.

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In a Cabot case, the patient was reported to have complained of stomach trouble for 15 years and for 1 year prior to operation had been unable to swallow solid food. Following removal of a pericardial cyst, the symptoms disappeared.[6] Lam reports a patient who had anginal symptoms so severe as to require morphine frequently and who had been almost bedridden for a year. Following removal of a pericardial cyst the patient resumed the normal life denied her during the preceding ten years.[12] In one of our patients (Case 2) an incapacitating recurrent paroxysmal tachycardia disappeared following the removal of the cyst. Thus, symptoms relative to the cyst are frequent.

TABLE I

YEAR	AUTHOR	CASES
1934	Pickhardt	1
1934	Weber and Schwarz	1
1936	Freedman and Simon	1
1937	Cabot Case No. 23492	1
1937	D'Abreau	2
1940	Addey	1
1940	Lambert	3
1941	Curreiri and Gale	1
1943	Greenfield, Steinberg, and Touroff	1
1946	Blades	10
1947	Bradford, Mahon, and Grow	8
1947	Lam	1
1947	Leahy and Culver	1
1948	Cooper, Archer, and Mapp	5
1949	Beck and Straub	1
1949	Gouraux, Jensen, and Morin	1
1949	Schein	1
1950	Buyers and Emery	1
1950	Conklin	2
1950	Drash and Hyer	5*
1950	Gillespie and Martinson	1
1950	Kisner and Reganis	1
1950	Lillie, McDonald, and Clagett	12
1951	Nichol and Dean	1
1951	Forsee and Blake	11†
	Total Cases	62

*All previously reported.
†Seven previously reported.

The roentgenologic appearance of a pericardial celomic cyst is reasonably characteristic. A round or ovoid, sharply demarcated, homogenous shadow occupying the angle between the cardiac silhouette and diaphragm anteriorly and not fluoroscopically separable from these structures is most suggestive (Figs. 1 and 2). On occasion, however, the cyst may lie in a supracardiac position.[6, 7, 11, 12] The fluoroscopic sign described by Lam as a change in the shape of the cyst with inspiration and expiration has not been observed by us.[12] A sphere containing the maximum volume that can be enclosed by a given surface area resists changes in shape.

The establishment of the diagnoses of many intrathoracic lesions including pericardial celomic cyst require thoracotomy. At operation the gross appearance of these cysts is characteristic, probably 90 per cent occupy the anterior cardiophrenic angle, they are movable, spherical, glistening, and transparent. They are covered by mediastinal pleura and are attached to the diaphragmatic or

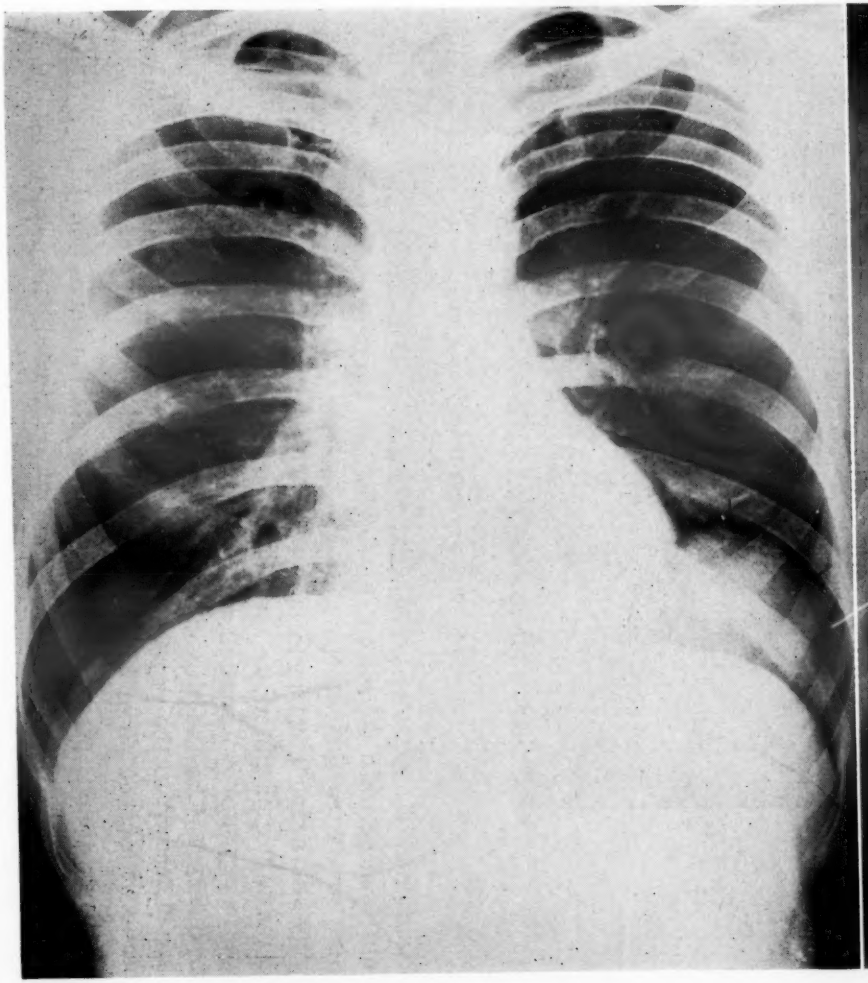

Fig. 1.

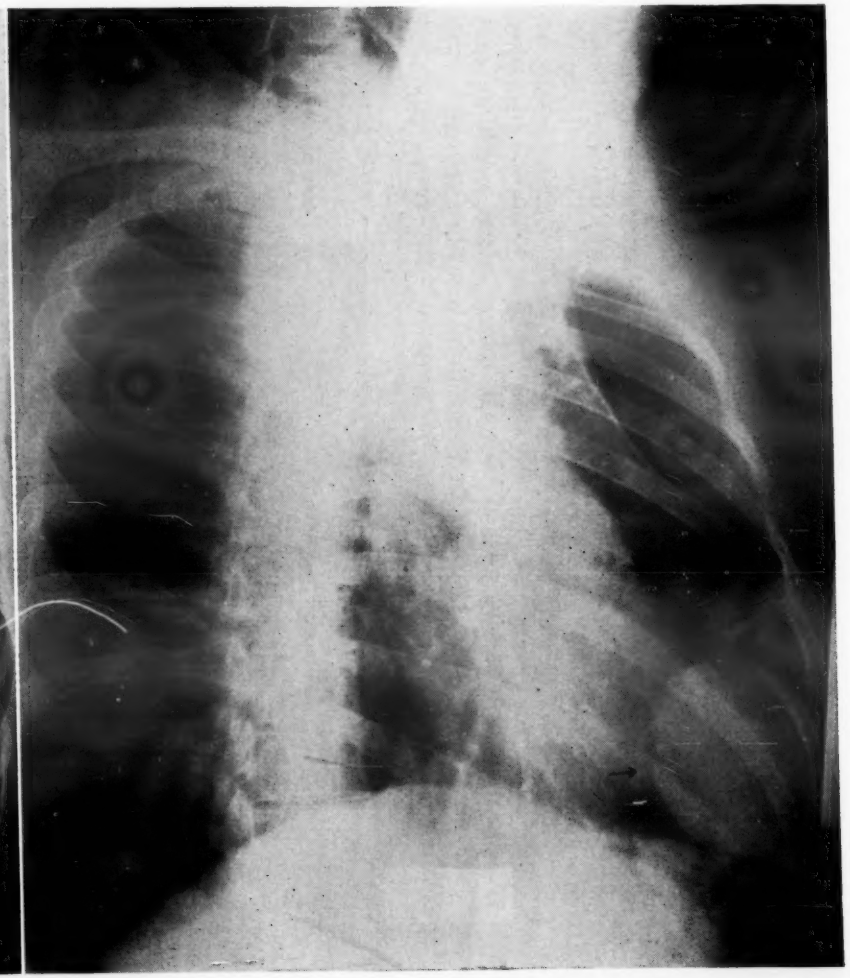

Fig. 2.

Fig. 1.—Classical posteroanterior roentgenogram of a pericardial cyst, left.
Fig. 2.—Right anterior oblique roentgenogram of the same pericardial celomic cyst as shown in Fig. 1.

pericardial surface by a relatively thin pedicle which contains the vascular supply to the cyst. The tense cyst contains a clear watery fluid which on analysis shows a low protein, a high sodium chloride value, and a specific gravity which has averaged 1.009. The cyst wall is paper thin and transparent (Fig. 3). The cysts usually are unilocular but occasionally may be multilocular. They are easily enucleated.

Microscopically, the cyst wall is not impressive. It is composed of either compact or loosely arranged strands of fibrous tissue, often acellular and hyalinized. Lymphocytes may be scattered through the fibrous wall. The lining membrane is indefinite and often completely destroyed. When visible it

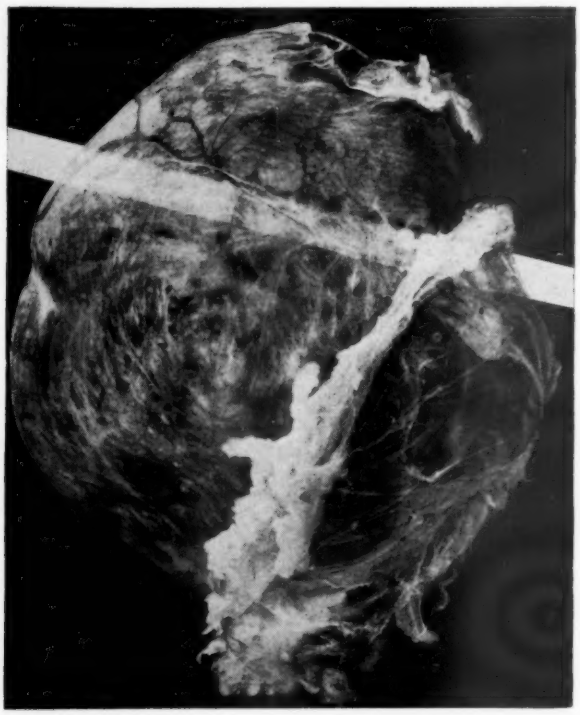

Fig. 3.—Unopened, fluid-filled cyst. Note spherical shape, clarity of fluid contents and transparency of the cyst wall. A white strip of paper is readily seen through the unopened cyst.

shows flattened or cuboidal mesothelial cells. An interesting correlation has been observed between growth of the cyst as seen by serial roentgenograms and flattening or destruction of the lining membrane. If the cyst appears to be enlarging the lining membrane may be cuboidal. If growth appears to have ceased the lining membrane is extremely flattened or destroyed (Fig. 4). The intracystic pressure is essentially a measure of the vertical height of the fluid within the cyst. As the size increases the intracystic pressure increases and acts as a deterrent to the growth of the cyst by pressure atrophy of the lining membrane with cessation of secretion.

In the treatment of pericardial celomic cysts temporization is ill advised. The relief of symptoms, whether organic or functional, the positive establish-

ment of the benignity of the lesion, and the low morbidity and mortality of the operative procedure warrant exploration.

CASE 1.—A 49-year-old white woman was admitted to Fitzsimons Army Hospital Aug. 21, 1948, after routine roentgenograms had shown a lesion in the right chest. The patient thereafter noticed exertional dyspnea and a sense of heaviness over the right hemithorax. The past medical history revealed "brain fever" at the age of 6 years. Physical examination was within normal limits. Laboratory studies were negative. Roentgenograms of the chest showed a round, smooth, discrete shadow in the right anterior cardiophrenic angle. Fluoroscopy failed to show a change in shape of the cyst upon inspiration and expiration. Exploratory thoracotomy was performed Sept. 2, 1948. A thin-walled, transparent cyst, 8 cm. in diameter, was removed from the right anterior cardiophrenic angle. The cyst was multilocular and contained 210 c.c. of clear fluid with a specific gravity of 1.008. Microscopically, the cyst wall was composed of a thin compact fibrous layer with scattered lymphocytes throughout the section. The lining membrane was destroyed. The postoperative course was smooth and for three years the patient has been relieved of the symptoms previously attributed to the presence of the pericardial celomic cyst.

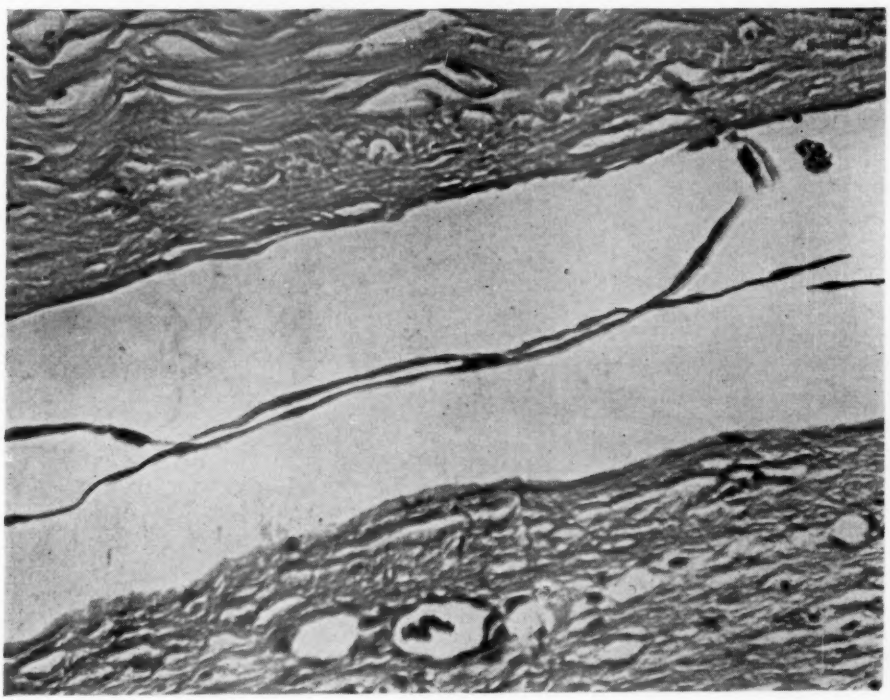

Fig. 4.—Photomicrograph of cyst wall showing flattening of lining cells.

CASE 2.—A 24-year-old white soldier was admitted to Fitzsimons Army Hospital March 22, 1950, with a complaint of attacks of fainting, dizziness, and shortness of breath associated with paroxysms of tachycardia. These attacks of paroxysmal auricular tachycardia occurred every two weeks and lasted approximately one-half hour. Because of persistence of the last such attack, the patient was hospitalized. The past history revealed a rib resection on the right at the age of 5 years for empyema. The patient had had severe bouts of pneumonia at the ages of 5, 12, and 17 years. Physical examination showed a slightly enlarged thyroid, moderate gynecomastia (left), and unilateral testicular atrophy (left). Laboratory studies and endocrine investigations were within normal limits. Chest roentgenograms showed a smooth, round, homogenous density lying in the right anterior cardio-

phrenic angle which was known to have been present for 3 years. Exploratory thoracotomy April 19, 1950, revealed a cyst, 7 cm. in diameter, in the right anterior cardiophrenic angle which was easily removed. The cyst was tense, glistening, and its wall was transparent. Clear fluid, 125 c.c., with a specific gravity of 1.014 was removed from the cyst. Microscopic section showed the wall to be formed by a loose fibro-fatty tissue with scattered lymphocytes and lined by low cuboidal cells with dark-staining nuclei. One year after surgery the patient had had only infrequent attacks of paroxysmal auricular tachycardia.

Fig. 5 (Case 4).—Lateral roentgenogram showing characteristic finding of pericardial celomic cyst.

CASE 3.—A 45-year-old white woman entered Fitzsimons Army Hospital June 19, 1950, after a routine roentgenogram of the chest had shown a round area of increased density in the right anterior cardiophrenic angle which had not changed in size during a year's observation. The patient had no symptoms and the past medical history was noncontributory. Physical examination and routine laboratory studies were normal. Fluoroscopy showed no change in shape of this lesion upon inspiration and expiration. Exploratory thoracotomy, July 7, 1950, revealed a cyst, 7 cm. in diameter, lying in the right anterior cardiophrenic angle, which was removed. The cyst contained clear fluid and its wall was paper thin. Microscopically the cyst wall was composed of a thin fibrous stroma supporting the flattened lining membrane. One year after operation the patient remained well and was most grateful for the establishment of the benign nature of the lesion and its removal.

CASE 4.—A 20-year-old white soldier entered Fitzsimons Army Hospital Aug. 5, 1950, with complaints of substernal pain of three months' duration, cough, and hemoptysis. Roentgenograms of the chest demonstrated a round, discrete lesion seen in the right anterior cardiophrenic angle (Fig. 5). Physical examination upon admission and routine laboratory studies were within normal limits. Fluoroscopy showed no change in the shape of the mass upon inspiration and expiration. Exploratory thoracotomy Sept. 19, 1950, revealed a cyst, 6 cm. in diameter, attached by a thin pedicle to the pericardium in the right anterior cardiophrenic angle. The cyst contained clear fluid and its wall was transparent. Microscopically, the lining membrane consisted of a single layer of flattened cells with large, dark-staining nuclei. The postoperative course was smooth; the patient returned to full military duty and one year later was in excellent health.

CONCLUSIONS

Reports of sixty-two pericardial celomic cysts which have been removed are found in the English literature.

Approximately two-thirds of the patients have symptoms which first attract attention to the cyst. Asymptomatic individuals often develop symptoms after learning of the cyst's presence.

Cysts located in the supracardiac position are likely to be misdiagnosed and more frequently produce disturbing symptoms.

Changes in shape with inspiration and expiration are rarely seen.

Although self-limiting and of themselves benign, positive differential diagnosis requires thoracotomy.

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BILATERAL CONGENITAL CLEFTS OF THE LOWER LIP

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CONGENITAL defects of the lower lip are not common. Apparently the most frequent variety is what is variously called "double lower lip," "pits of the lower lip," "congenital fistula," "paramedian sinus."[5] Davis,[3] in reporting 1,000 cases of congenital deformities of the face, found 14 such cases, but makes no mention of a cleft of the lower lip. Thoma[10] states that "cleft of the lower lip is extremely rare." He pictures one case, reported by Stewart[9] in which the cleft is median and associated with incomplete union of the mandible.

The case reported here is unusual and we have been unable to find any description of an exactly similar one.

The patient was a newborn white female infant, admitted with the defects pictured (Fig. 1). There were three distinct congenital defects. The first defect consisted of an elongated, snoutlike process, measuring 3 by 1 cm. and 0.08 cm. thickness. It arose from the junction of the anterior and middle third of the hard palate, and protruded out the mouth. The second defect was an ankyloglossia, a fusion of the anterior end of the inferior surface of the tongue with the inferior gingival border. The third, and most interesting defect, concerned itself with the lower lip. It apparently consisted of a bilateral cleft in the lower lip extending through ¾ the width of the lower lip, and with a knoblike mass of tissue measuring 3 by 2 by 1.5 cm., occupying the area between the two clefts. X-ray examination of the mandible (Fig. 2) showed separation of the mandibular bones in the midline.

Operative Procedure.—Five days postnatally the infant was operated upon. Under general anesthesia, the process from the hard palate was removed flush with the hard palate, no attempt being made to cover the 2 to 3 mm. area of denuded hard palate. No hard palate defect was present. Then the tongue was freed up from the gingival border and the under surface sutured together to cover the raw surface. Finally, the lower lip was freed from the gingival border with an incision in the labiogingival groove. The excess tissue in the mid-portion of the lip was excised, and primary closure of the defect in the lower lip was effected. A Logan's bow was applied. Healing was satisfactory, with the result pictured in Fig. 3. Some correction of the notching in the lower lip will be necessary subsequently.

The intriguing problem, of course, is the nature of the defects. Our first impression was that there were two parasitic monsters growing, one from the hard palate, one from the lower jaw. The tissues on section were reported as follows: that from the hard palate was stratified squamous epithelium overlying bone, embryonal cartilage and tooth bud (Fig. 4). This very probably does represent a parasitic monster, an epipalatus. This would conform to Arnold's Group 1,[1] or minimally differentiated oral parasite.

The microscopic report on the mass of tissue excised from the lower lip was that it showed a tooth bud partially covered by stratified squamous epithelium (Fig. 5). Other sections showed the soft tissue normally found in the

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Fig. 1.—Preoperative appearance.

Fig. 2.—Roentgenogram of mandible.

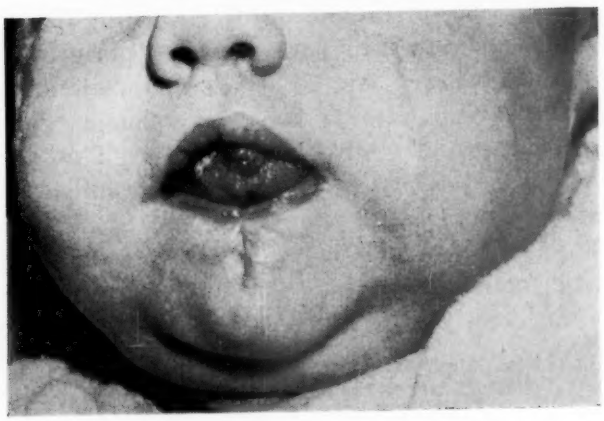

Fig. 3.—Postoperative appearance.

Fig. 4.

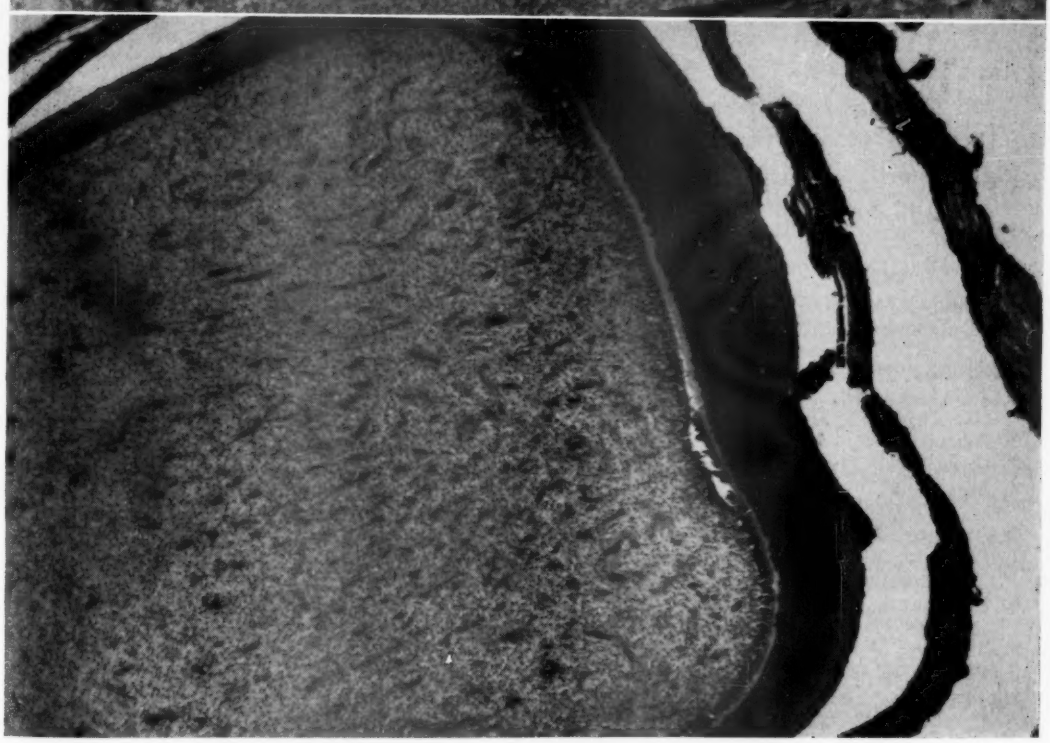

Fig. 5.

Fig. 4.—Photomicrograph of process protruding from hard palate.
Fig. 5.—Photomicrograph of tissue from median portion of lower lip.

lower lip. It was felt it was not a parasitic monster. Then how to explain its origin, this bilateral cleft of the lower lip with the central mass of excessive tissue? Perhaps the central mass represented a compensatory overgrowth due to the presence of the clefts, such as is seen in the premaxilla in case of bilateral clefts of the upper lip.[26]

It would be difficult, however, to explain the bilateral clefts on the basis of the usual conception of facial embryology: i.e., 5 processes fusing together. Thus in the lower lip, there are supposed to be two mandibular processes approaching each other and fusing across the midline. Such an embryological concept explains such a case as reported by Stewart, but does not offer any logical explanation for a bilateral lower cleft. However, as Cannon and associates[2] point out, doubt about the theory of "fusion" was raised back in 1910 as the result of the studies of Pohlmann[8] and Veau.[11] Their studies indicate that actually an ectodermal "hood" develops over the front of the oral cavity adjacent to the primitive nostrils. These ectodermal tissues are invaded by mesoderm from the edges of the oral cavity, forming the lips, etc. They believe that development of clefts of the lip, etc., is the result of incomplete or absent penetration of the ectodermal wall by mesodermal tissue. With no mesodermal supporting tissue, the ectodermal tissue ruptures and a cleft is formed. Only by such a theory can bilateral clefts in the lower lip be explained on a developmental basis.

SUMMARY

1. An unusual case of congenital defects about the mouth of a female infant is reported.

2. It is thought the case consisted of (a) a parasitic monster (epipalatus) of the hard palate, (b) ankyloglossia, or fusion of the tongue with the lower gingival border, and (c) bilateral clefts of the lower lip.

3. The result of surgical correction is pictured.

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Editorial

The Importance of Enzymes in Surgery: Mechanisms of Survival

THE ability of man to survive injury is the foundation upon which the practice of surgery has been established. This capacity varies in different individuals and even in the same individual from time to time. Logic and experience dictate that there must exist causes for these differences. Some of these causes are perhaps as fundamental as life itself, but others are being identified. It has been abundantly established that injury results in a characteristic pattern of neuroendocrine activity which enhances the resistance of the individual to trauma. This activity affects such processes as fat, carbohydrate, protein, fluid and antibody metabolism. The mechanisms by which these beneficial hormonal effects are realized are of both practical and theoretical interest.

It is no longer enough to state that hormones "excite various organs to activity." It is increasingly evident that most hormonal actions will eventually find their proximate explanation in appropriate enzyme systems, but, as yet, the outlines of this control are still dim. The study of enzymes, probably the central field in current biochemical research, is by no means a new field of investigation; sound work was done in the latter part of the nineteenth century. It is, rather, the number and the complexity of enzymes (which already are numbered in the hundreds) which make it difficult to visualize the total picture. Nevertheless, many enzymatic processes have been harnessed for practical use. An increase in serum amylase strongly supports the diagnosis of acute pancreatitis. An increased serum acid phosphatase level is practically diagnostic of carcinoma of the prostrate with bone metastases; this level may fall to normal as the beneficial effects of castration and/or estrogen therapy are realized, only to rise again as such therapy wanes in effectiveness. An elevated serum alkaline phosphatase level is helpful in the diagnosis of such conditions as obstructive jaundice and parathyroid adenoma. A diminished pancreatic enzyme content in the succus entericus is evidence of pancreatic disease. Streptokinase and streptodornase are useful in liquefying intrapleural clots. Thus, surgeons commonly employ certain enzymes in the conduct of their practice.

What is the evidence that enzymes are controlled by hormones? It has been intimated previously that the hormonal support in stress is probably mediated through an effect upon rates of activity of enzyme systems. The strongest basis for this assumption is the demonstration by Cori that the activity of hexokinase, which catalyzes an essential intermediate step in the oxidation of glucose to water and carbon dioxide, is controlled by insulin and

a pituitary antagonist. If hexokinase cannot act, glucose is not utilized normally and the manifestations of diabetes appear. Other types of evidence indicate a close relationship between hormones, enzymes, and vitamins. Cytochrome C is an important respiratory enzyme concerned with the cellular utilization of oxygen; Drabkin has shown that the tissue concentration of this enzyme can be reduced by thyroidectomy or by the administration of thiouracil. Cortisone has been shown to have a marked inhibitory effect on hyaluronidase.

What is the evidence that enzymes are involved in mechanisms of disease? To implicate enzymes in mechanisms of disease it is necessary to present evidence that specific enzymatic activities are altered in specific disease states. This can be done. It has been noted that serum levels of amylase, acid phosphatase, and alkaline phosphatase are altered under specific disease conditions. Other examples may be cited. While there is a progressive increase in the serum glucuronidase during pregnancy, this enzyme is even more increased in eclampsia. It is not significantly increased in hypertensive toxemia. The source of this increase in glucuronidase is not known. There is a decrease in proteolytic enzymes, but an increase in serum fibrinolytic activity in toxemia of pregnancy. The invasiveness of streptococci is related to the activity of streptococcal fibrinolysin and its capacity to activate certain proteolytic enzymes of plasma.

As with most life processes, there exists a system of checks and balances in enzyme activity. The action of many enzymes has been shown to be opposed by antagonistic substances. For example, a rise in serum hyaluronidase inhibitor usually follows the wounding of an animal. The mechanism involved in anaphylactic shock and other allergic phenomena is thought to be enzymatic in nature. The consensus is that histamine is liberated through the activation of proteolytic enzymes and that the histamine then prevents other enzymes from functioning normally. This hypothesis stimulated the search for substances similar in structure to histamine which would act as histamine antagonists in allergy states, and Benadryl and Pyribenzamine have been found to be useful in this regard. Once again theoretical concepts have resulted in practical therapy.

Why are vitamins vital? A number of the better known vitamins have been shown to be necessary components of enzyme systems. Thiamine is a part of the molecule of co-carboxylase, which in the brain catalyzes pyruvic acid to acetic acid. When this reaction cannot proceed, beriberi results with its characteristic central nervous system manifestations. A diet deficient in the vitamin pyridoxine has been shown to lower the amount of co-enzyme in the tissues, and the abnormal amino acid metabolism which results is reflected in the urine. This is reversible by the administration of the vitamin. Pantothenic acid is a part of a co-enzyme concerned particularly with the formation of acetylcholine, the important chemical substance concerned with the transmission of neural impulses. Riboflavin is a part of a group of "yellow" enzymes which are involved in biologic oxidation reactions. Finally, para-aminobenzoic acid is considered to be a part of an enzyme system which is necessary for bacterial growth. The bacteriostatic action of sulfonamides is effected through the substitution of the sulfa drug at the position in the enzyme molecule pre-

viously occupied by para-aminobenzoic acid, rendering the enzyme ineffective. There is, as yet, no solid evidence that penicillin and streptomycin act in a similar way, but it is strongly suspected that they do.

It may be noted here that some metals are essential elements of certain enzyme molecules. For example, cytochrome contains iron. Carboxylase contains magnesium and co-carboxylase contains phosphorus, both of which enzymes are concerned with carbohydrate oxidation in the brain. Copper is probably an essential element in an enzyme active in the formation of hemoglobin.

When does survival begin? Returning to the variations among individual patients in their capacity to withstand trauma, it is necessary to consider the probable origin of enzymes. In broad outline, a person's resistance may be determined by his parents. The innumerable genes contained in the forty-eight chromosomes are believed to produce the enzyme pattern characteristic of the individual. In support of this view, artificially produced mutations result in altered genes, which in turn result in an altered enzyme pattern. Certain hereditary defects in metabolism which result from defective genes and thus enzymes are well known: albinism, where phenylalanine is not converted to melanin; alkaptonuria, where homogentisic acid is excreted in the urine, which turns black on standing; and phenylketonuria, where phenylalanine metabolism is deranged and a mentally defective person results. All three of these conditions are the result of abnormal genes, which produce abnormal enzyme activity. The products formed in different cells will often be characterized by the particular enzymes which they possess because it is these enzymes which help to manufacture the finished material. Yet, the enzymes themselves have first to be manufactured, and there is good reason to believe that the genes have a part in this process.

The healthy young adult has been considered the prime operative risk. The very young and the very old have been found somewhat less able to withstand the trauma of anesthesia and operation. There is suggestive evidence for an enzymatic explanation of this. Jones and McCance found the activities of erythrocyte cholinesterase, glyoxalase, carbonic anhydrase, and catalase significantly higher in adult than in umbilical cord blood. Erythrocyte acid phosphatase activity was essentially the same in the two groups. Carbonic anhydrase activity has been found to be lower in infant than in adult red cells and still lower in premature infant red cells. These observations, taken together with the fact that cord red cells disappear at nearly twice the rate in the infant circulation that adult red cells disappear in the first ten days following infusion, suggest reasons for the variations found in the life span of stored red cells from different individuals. Meyer, Spier, and Neuwelt studied the basal secretion of certain digestive enzymes in old age and found a deficiency in the concentration of salivary amylase and a diminution in both the proteolytic enzymes pepsin and trypsin. Blood arginase activity, however, has been found so constant in the given individual as to "indicate that it is controlled largely by genetic factors and relatively uninfluenced by dietary or endocrine vectors." The average blood arginase activity is higher for females than for males, and this is so even before puberty. In general, then, there exists already

good evidence that enzyme activities vary in children, young adults, and the very old. It is not unlikely that such factors will be shown to be important in the quantitative aspects of resistance to stress.

Additional avenues for investigation. It would appear inescapable that surgical thought must probe deeper for the explanations of such complex problems as shock, burn toxemia, late intestinal obstruction, anesthesia intolerance, mechanisms of bacterial invasion, and malignancy. It is submitted that a careful survey of enzymes already identified may supply new leads.

—*James D. Hardy, M.D.*

Recent Advances in Surgery

CONDUCTED BY ALFRED BLALOCK, M.D.

EXPERIMENTAL MAINTENANCE OF THE CIRCULATION BY MECHANICAL PUMPS

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THE investigations to be reported in this communication have been concerned with by-pass of the heart in the dog by mechanical extracorporeal pumps using the dog's own lungs as the means of oxygenation of the blood. The problem of by-passing the heart alone involves the use of two pumps. One pump is interposed between the systemic venous return to the right side of the heart and the lungs in order to replace the right heart while the other pump replaces the function of the left heart by pumping the venous flow from the lungs into the systemic arterial circuit. Among the first to construct mechanical hearts to be used in series with the animal's own lungs were Gibbs[7, 8] and Dale and Schuster.[2] The former developed a pump of the bellows type while Dale and Schuster constructed a mechanism involving an alternately inflating-deflating finger cot mechanism. Recently other investigators[12-14] have reported their experiences using simple pump by-passing of either the right or left side of the heart. The pump to be described has features of both of the early types of pumps (Gibbs and Dale and Schuster) combined with some unique features developed in our laboratory. The advantage of simple heart by-pass lies in the preclusion of an artificial oxygenator since the animal's own lungs are used as the means of oxygenation. Machines devised to by-pass blood around both the heart and lungs require an artificial extracorporeal oxygenator for the circulating blood. Gibbon and associates,[4-6, 15] Dennis and associates,[3] Björk,[1] and Jongbloed[11] have been the principal investigators in this field. Theoretically these mechanisms have an advantage over simple pumps in that thoracotomy or other major surgical intervention is not needed. Unoxygenated venous blood is withdrawn from the jugular vein in the neck and pumped into the femoral artery after oxygenation outside the body. The pump-oxygenator, therefore should be of more practical value as an aid to the failing heart. Its disadvantage lies in the necessity of an oxygenator. To date because of the inherent problems

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of artificial oxygenation of blood in quantity, pump-oxygenators have had only limited success in allowing regular recovery of the experimental animals subjected to by-pass of both heart and lungs.

In the field of elective cardiac surgery, however, there is no good reason why simple heart by-pass may not be useful since thoracotomy must be carried out for intracardiac surgery. Certainly the organism's own lung is an ideal oxygenator. In our work the technical difficulties of cannulating the pulmonary flows have been overcome to the degree that the application of simple heart by-pass to the field of bloodless experimental intracardiac surgery is quite promising.

AIMS OF THE PROJECT

Work in this laboratory began with the use of a primitive artificial heart developed by Halkett and Sewell.[9] Results of preliminary experiments by Halkett, Hackworth, Etsten, and Morris[10] in our laboratory were sufficiently good to proceed with a formal project, the aims of which were as follows: (1) the construction of a reliable standard pump capable of delivering 6 liters of blood per minute in divided quantities at rates from 120 to 160 strokes per minute without foaming of blood or fibrin deposition and with minimal hemolysis; (2) the perfection of techniques for complete functional replacement of the left and right heart individually for periods of from 1 to 2 hours with regular survival of animals (dogs); (3) the perfection of complete replacement of the function of the entire heart with simultaneous artificial maintenance of both the lesser and greater circulation with regular recovery of animals (dogs); (4) the application of the pump mechanism to experimental intracardiac operations; (5) the study of the systemic and pulmonary circulations using the mechanical pump without the intermediation of the normal heart; (6) the production of experimental cardiac diseases in dogs. This communication is a report of our experience with functional replacement of the heart by pumps.

THE EXTRACORPOREAL PUMP APPARATUS

Fig. 1 is a schematic drawing of the pump. Two identical pumps are used when the function of both sides of the heart is replaced. The principal components of the pump mechanism require detailed description if functional replacement is to be understood. It is most convenient to begin the description of the pump at the reservoir.

The Reservoir.—Each reservoir is constructed of a Lucite cylinder with an internal diameter of 7.6 cm. It corresponds to a cardiac atrium and has a calibrated capacity of 550 c.c. During pump activity the reservoir holds from 100 to 400 c.c. of blood. Within the reservoir there is at all times an air pocket which acts as a buffer to minimize reservoir pressure changes which occur with changes in the blood level. The *input lead* delivers blood from the venous cannula in the animal into the reservoir. The orifice of the input lead is kept submerged to prevent foaming of blood. There is a filter of fine mesh Monel metal screen over the reservoir end of the input lead. This filter strains out clots and incidental air bubbles. Three baffles are placed between the input

filter and the outlet to augment the removal of air bubbles. The bottom of the reservoir slants toward the outlet to facilitate flushing and cleaning. A side arm of the input lead is connected to an overhead tank which is used as an auxiliary reservoir for adding blood to the pump for priming or for transfusions during pump activity. Both the reservoir and overhead tank are calibrated in cubic centimeters for purposes of recording the quantity of blood infused into the experimental animal. The pressure of the air pocket within

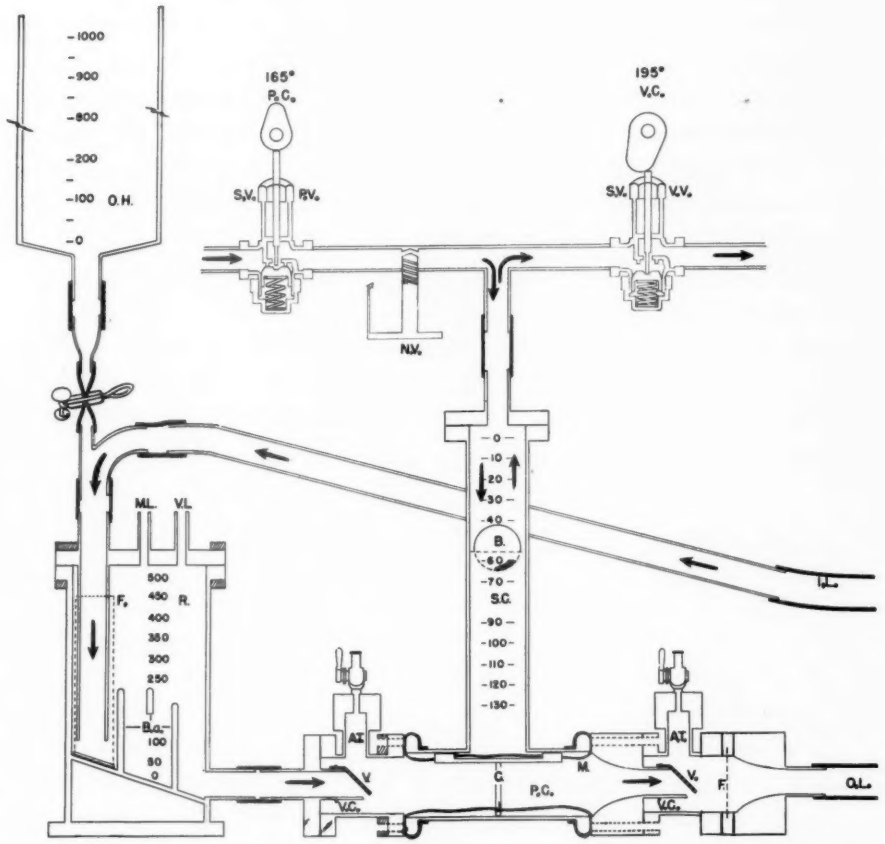

Fig. 1.—Schematic diagram of the extracorporeal pump apparatus. *A.T.*–air trap, *B.*–cork ball, *B.a.*–baffles, *C.*–stainless steel cage, *F.*–Monel screen filter, *I.L.*–input lead, *M.*–rubber membrane, *M.L.*–manometer lead, *N.V.*–needle valve, *O.H.*–overhead reservoir, *O.L.*–output lead, *P.C.*–pump chamber, *P.C.* (upper part of diagram)–pressure line cam, *R.*–reservoir of the pump, *S.C.*–stroke chamber, *S.V.P.V.*–steam valve interrupting the air pressure line, *S.V.V.V.*–steam valve interrupting the air vacuum line, *V.*–flap valve, *V.C.*–valve chamber, *V.C.* (upper part of diagram)–vacuum line cam, *V.L.*–auxiliary reservoir pressure regulator lead. (Reproduced through the courtesy of W. B. Saunders Company.)

the reservoir is measured by means of a mercury manometer fitted with an air trap for the reading of negative pressures. During pump activity the reservoir pressure is kept constant by means of an auxiliary reservoir pressure regulator. Latest studies show that the reservoir pressure during pump activity should be maintained at minus 30 mm. Hg pressure.

The Valves.—After investigating various types of valves it was found that the simple flap valve was the most efficient. The "raspberry" type valve was

found to be unsuitable because it inverted within its own lumen when subjected to the pressures used in this mechanism. Other types of valves studied were found unsuitable because they either caused too much hemolysis or they offered too much resistance to the flow of blood through them with a resulting decrease of pump efficiency. The flap valve is of simple construction. It is durable and in spite of its rubber construction has not produced fibrin deposition. By cutting the valve seat 20 to 30 degrees off the vertical angle regurgitation has been minimized and the efficiency of the valve increased. Actual construction of the flap valve involves cementing two small oval pieces of rubber around a thin oval of metal sheeting. The tongue that projects from one of the rubber ovals is used to fasten the valve to its seat. This tongue has a light spring action tending to close the valve. One valve is placed at either end of the pump chamber. Both valves open only toward the output of the pump and allow filling of the membrane in the pump chamber only from the reservoir and emptying of the membrane only into the output lead. Each valve is situated within a valve chamber which is fitted with an air trap and stopcock to allow removal of air in the pump especially during priming.

The Pump Chamber.—The membrane through which blood flows from the input valve to the output valve is the cavity of the artificial ventricle and is contained within the pump chamber. It is a segment of Gooch tubing which is placed within the lumen of the pump chamber and stretched over each flanged end. The pump chamber consists of a T-shaped cylinder of Lucite which is 11.5 cm. long with an internal diameter of 3.8 cm. The upright cylinder cemented at right angles to the pump chamber is called the stroke chamber. Water is placed in the stroke chamber and a cork ball is floated in the water. The stroke volume can be read directly by noting the excursion of this cork ball on the calibrated scale on the side of the stroke chamber. The force which drives this stroke chamber so as to alternately compress and expand the rubber membrane within it has been described elsewhere.[16, 17] It consists of alternate positive-negative air pressures which are applied to the supernatant air in the stroke chamber and act as an air piston. Twenty inches of mercury vacuum is applied during 195 degrees, and 15 lbs. per square inch pressure is applied during the remaining 165 degrees of each pump cycle. The stated dimensions of the pump chamber were found to be optimum for maximum output with the pressures concerned. Pump chambers of smaller dimensions were found to give an insufficient stroke for our purposes because they did not possess sufficient capacity. Larger sized pump chambers did not exhibit sufficient minute output at the rates desired because of excessive inertia of the liquid in the system.

Filters.—There are two filters used in the system. One is situated about the input lead of the reservoir as previously mentioned and the other is placed just distal to the output valve of the pump. Both filters are made of fine mesh screening of Monel metal. The spaces in the screening are rectangular and measure approximately 200 by 300 μ. With the dosage of heparin used, the filters have been found to cause no fibrin deposition. Neither filter is considered

necessary. In some experiments replacement of the function of the left heart was carried out for a period of 1 hour without the filters. The animals recovered with no postoperative evidence of embolism.

Leads.—The ouput lead from the pump to the arterial cannula in the animal consists of pressure-resistant gum rubber tubing. The input lead from the venous cannula in the animal to the reservoir is made up of rubber and glass tubing.

General Remarks.—Streamlining of the lumen of the pump, especially on the output side of the rubber membrane, has been found to add to the efficiency of the pump. The inner lumen of the pump mechanism which comes in contact with blood has not been siliconized. Attempts have been and are being made to minimize mechanical damage to the red cells by all other means before this step is taken. Each pump has a maximum output of 6,000 c.c. of blood per minute against an artificial peripheral resistance of 140 mm. Hg at pump rates of from 120 to 160 strokes per minute. Each pump requires 900 c.c. of blood for priming. Models of smaller capacity are being designed.

THE CANNULAE

If the function of both sides of the heart is to be replaced, four cannulations must be carried out. After investigating various sites for cannulation and a variety of sizes and shapes of cannulae, four standard cannulae were developed. The sites of cannulation for replacement of the right heart are at the external jugular vein for collection of caval blood and at the left pulmonary artery via a left-sided thoracotomy for delivery of caval blood to the lungs. For replacement of the left side of the heart the left auricular appendage and the left brachial artery are cannulated for shunting blood from the lungs to the systemic circulation. Both of these maneuvers are performed by left-sided thoracotomy. Thus, bilateral cardiac replacement is accomplished by unilateral thoracotomy on the left side plus a neck incision for jugular cannulation.

The Caval Cannula.—This cannula collects the input for the right pump. It is constructed of thin-walled polyethelene tubing which has multiple perforations along its distal inch in addition to an end hole. It is 25 cm. in length and of 8 mm. outside diameter. It is inserted through the left external jugular vein at the base of the left neck and threaded through the innominate vein and superior vena cava until its tip lies within the right atrium. It is tied in place by means of a ligature about the wall of the left external jugular vein.

The Left Pulmonary Artery Cannula.—This cannula delivers the output of the right pump into the pulmonary circuit for oxygenation in the lungs. It is a specially designed glass T tube. The shaft of the T is 9 mm. outside diameter while the outside diameter of the crossbar of the T is 7 mm.. The limbs of the crossbar are of unequal length, the longer one being 6 mm. long and the shorter, 3 mm. long. At each extremity of the crossbar there is a circle of small glass beads to prevent slipping of the cannula when tied in place. The long limb of the T is first inserted through a transverse incision in the wall of the left pulmonary artery. The opposite edge of the incision is

pulled up over the short limb of the cannula much as a cap is pulled down over the eyes. Each limb is tied in place by means of a ligature around the wall of the artery. The insertion of a T-type cannula enables the use of both lungs for purposes of oxygenation without entry of the main pulmonary artery.

The Left Atrial Cannula.—This cannula collects the input for the left pump. It is made of glass tubing of 13 mm. outside diameter and is crescentic in shape. There is a hole at its distal end with multiple side-wall perforations in its terminal inch. It is inserted through the left auricular appendage into the left atrium and ligated in place by means of a ligature about the wall of the appendage.

The Left Brachial Artery Cannula.—This cannula delivers the output of the left pump into the aorta. It is made of glass tubing of 9 mm. outside diameter and is in the shape of the letter "C." It has a single distal perforation with glass beadings at the end. It is inserted into the proximal stump of the left brachial artery (analogous to the human left subclavian artery) near its origin from the arch of the aorta. This cannula allows sufficient flow of blood to satisfy the demands of the entire systemic circulation.

CANNULATION TECHNIQUE

The left side of the thorax is entered by resection of the fifth rib and costal cartilage. One or more costal cartilages may be sectioned anteriorly if greater exposure of the heart is needed. The cannulations need not be done in the order in which functional replacement is initiated. All four of the cannulae can be placed without actual blood flow through them for periods of an hour or more without disturbing the dynamics of the heart. After the four cannulation sites are dissected and prepared to receive their respective cannulae, a loosely placed umbilical tape is passed around the main pulmonary artery. Ten per cent procaine is injected into the pericardial sac to aid in preventing arrhythmias. Two milligrams of heparin per pound of body weight are administered intravenously to the experimental animal at this point. The cannula is placed in the left brachial artery and connected to the output lead of the left pump (Fig. 2). The left pulmonary artery cannula is inserted and connected to the right pump output lead (Fig. 3). The left atrium is then cannulated (Fig. 4) and the left pump is begun until a maximum stroke volume has been attained. A constant negative pressure of 30 mm. Hg is applied to the left reservoir to ensure complete diversion of the blood flow from the left atrium into the left pump reservoir. The stroke volume is adjusted to maintain a constant left reservoir level. The caval cannula is inserted through the left external jugular vein and is connected to the input lead of the right pump (Fig. 5). The right pump is begun. When the maximum stroke on the right side has been attained by the gradual opening of the stroke regulating needle valve, 30 mm. Hg constant pressure is applied to the right pump reservoir. The stroke volume is varied to maintain a constant right reservoir level, assuring equality of input and output of the right pump. At this point the function of the heart in maintenance of both the lesser and greater circulation is completely replaced by the mechanical pumps. The minute volume can be

easily computed by multiplying the rate of the pump in strokes per minute by the stroke volume which is read directly from the wall of the stroke chamber. The experimental dogs varied in weight from 22 to 56 pounds while the minute volume of each side of the pump varied from 1½ to 3½ liters per minute.

In the series of experiments presented in this communication functional replacement of the heart was carried on for periods of from 1 to 2 hours. After this period of time the cannulae were serially removed. Following removal of the left atrial cannula the left auricular appendage is simply ligated at its base with umbilical tape. The left brachial artery is doubly ligated at its

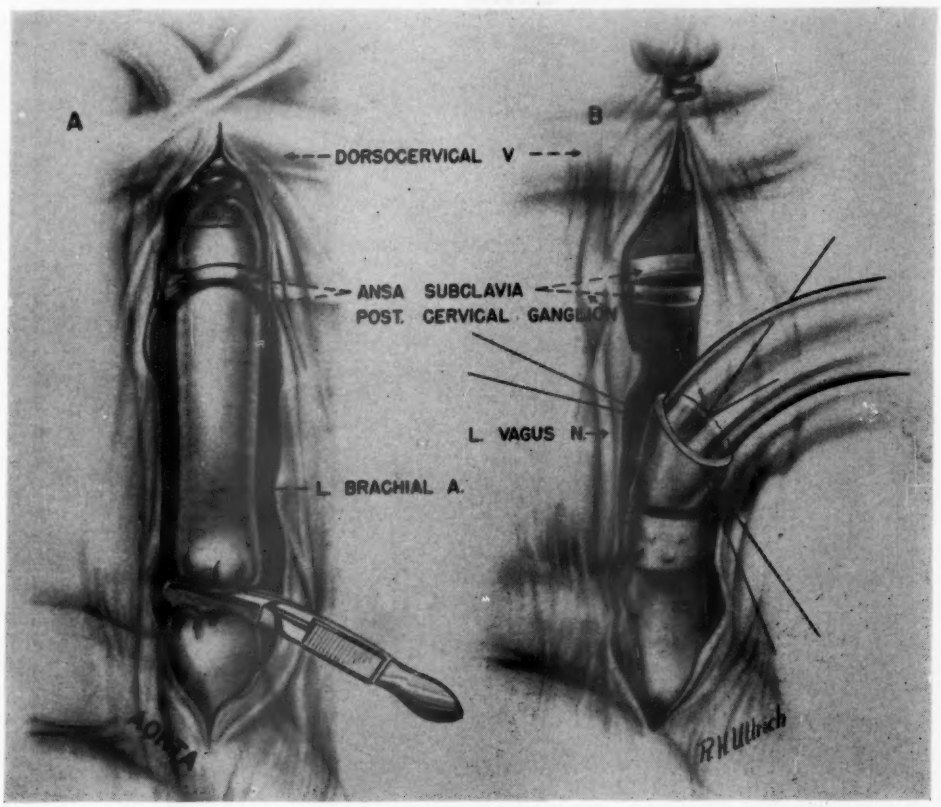

Fig. 2.—The cannulation of the left brachial (subclavian) artery. In *A* the artery has been doubly ligated at the site of branching and occluded with a sereffine clamp near its origin. The dotted line indicates the site of transection. In *B* the cannulation is completed. The tip of this cannula lies within the left brachial artery.

origin and the cannula removed with the excess cuff of artery. The caval cannula is removed and the left external jugular vein is ligated. The left pulmonary artery cannula is removed and the defect is repaired with 000000 arterial silk. The systemic blood pressure remains adequate during the entire procedure of replacement including the crucial periods of initiation and cessation of pump activity. Protamine sulfate is given intravenously to neutralize any circulating heparin. When the chest is essentially 'dry'' the operative wounds are closed. Obtaining a ''dry'' chest before closure is related to the return of the clotting time to normal and obtaining exact hemostasis by ligature.

DYNAMICS OF THE ARTIFICIALLY MAINTAINED CIRCULATION

Path of Blood in the Artificially Maintained Circulation

In the undisturbed circulation the blood from the venae cavae and coronary sinus is collected within the right atrium and passed through the tricuspid valve into the right ventricle, there to be ejected into the main pulmonary artery

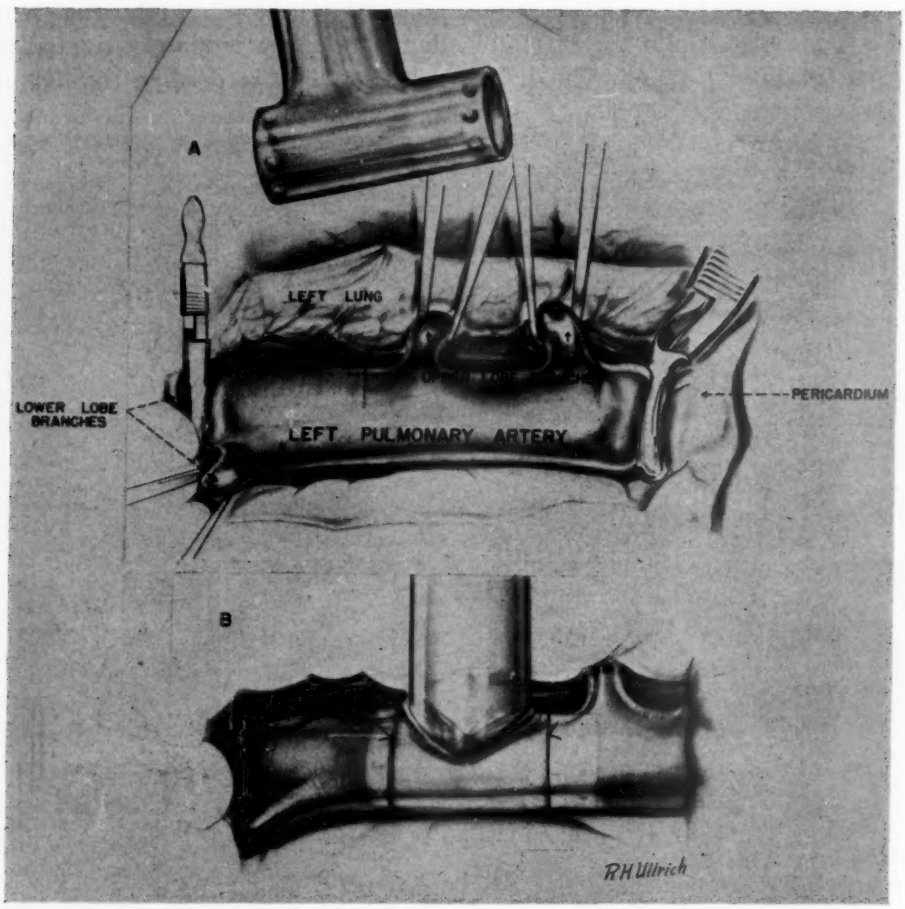

Fig. 3.—The technique of cannulation of the left pulmonary artery. In *A* the two upper lobe and first lower lobe branches are occluded with umbilical tape while the artery is isolated from the main flow by sereffine clamps. The dotted line indicates the site of incision for insertion of the T cannula. In *B* the cannulation is completed with removal of the sereffine clamps and umbilical tapes. The cannula is ligated into place on each side of the main shaft.

which supplies both lungs. The blood is oxygenated in the lungs and returned to the left atrium via the pulmonary veins. Oxygenated blood then passes through the mitral ring into the left ventricle which ejects the blood into the aorta and supplies the entire systemic circulation. During complete functional replacement of the heart by the pumps the blood from the superior vena cava, inferior vena cava, and coronary sinus is diverted from the right atrium into the right pump reservoir along a negative pressure gradient obtained by exerting a constant negative pressure of 30 mm. Hg within the reservoir of the right pump. The right pump then ejects this blood through a cannula in-

serted in the left pulmonary artery. Since this cannula is a T tube, blood is pumped through one limb of the T into the left lung and through the other limb of the T into the right lung. The lungs oxygenate the blood which is returned by the usual route to the left atrium. The oxygenated blood is

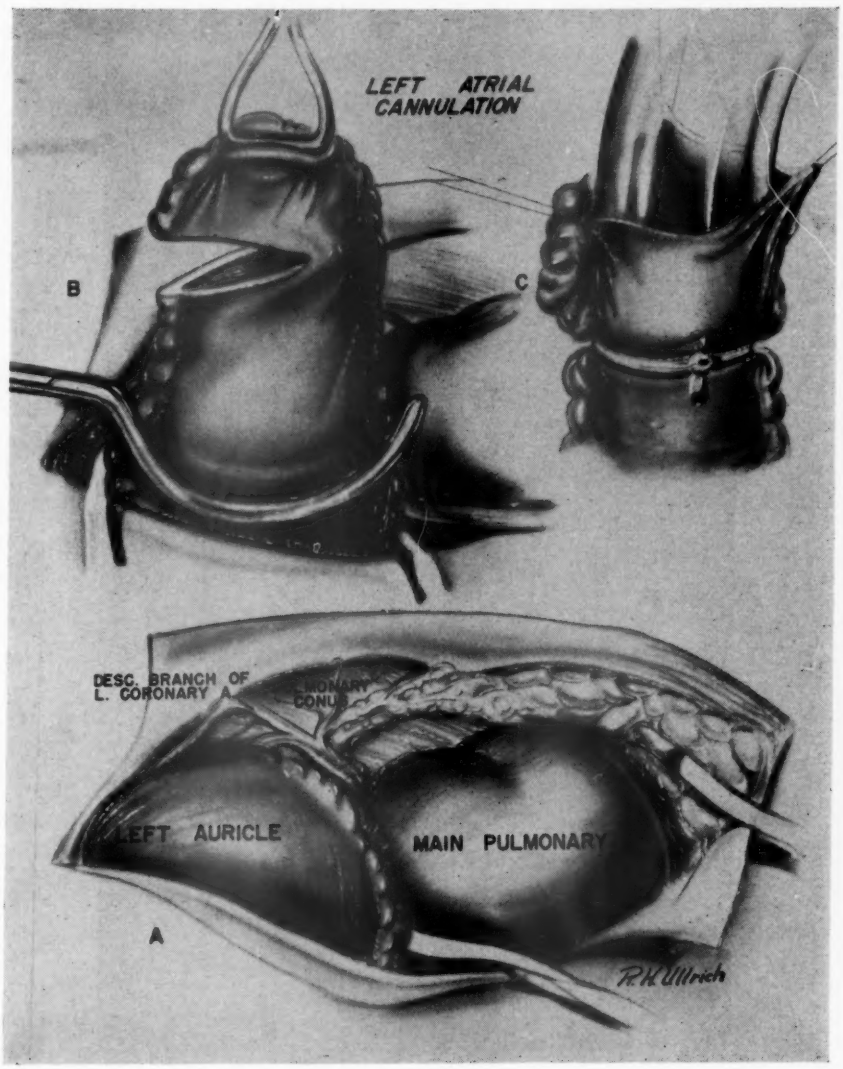

Fig. 4.—The cannulation of the left atrium. In *A* the pericardium is incised exposing the left atrium and main pulmonary artery. About the latter is an umbilical tape which will be used to occlude this vessel during functional replacement of the heart. In *B* a modified Satinsky clamp is used to occlude the auricle at its base while the tip of the appendage is being amputated. The trabeculae which must be severed to allow passage of the cannula are not shown. In *C* the cannulation is completed and the cannula is ligated into place with umbilical tape. The tip of the cannula lies within the left atrium.

diverted from the mitral orifice into the left pump reservoir through a cannula inserted into the left artium along a pressure differential obtained by a constant negative pressure in the left pump reservoir. The left pump ejects the blood in pulsatile fashion through the left brachial artery cannula into the aorta. Part of the brachial cannula flow passes retrograde toward the

heart to supply the circulation to the head and neck and coronary vessels. The rest of the left pump flow passes peripherally from the left brachial artery to supply the remaining systemic circulation. The altered path of the blood during by-pass of the heart is shown in Fig. 6.

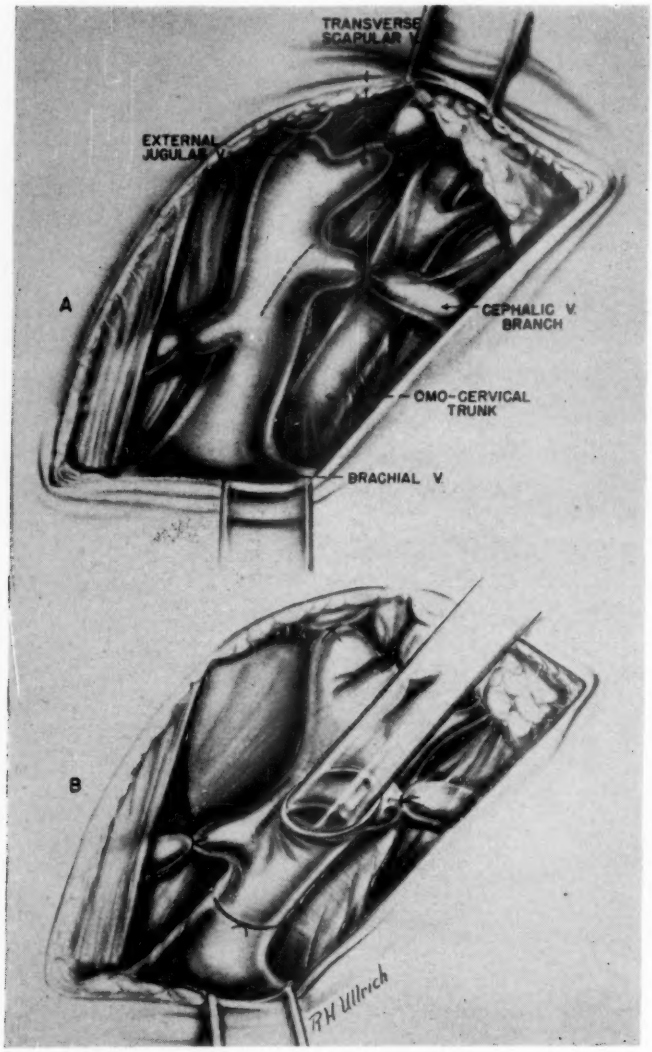

Fig. 5.—The technique of cannulation of the right atrium via the left external jugular vein. In *A* the dissection has been completed through a transverse incision at the base of the left neck. The dotted line indicates the incision for insertion of the cannula. In *B* the cannulation is completed. The tip of the cannula lies within the right atrium.

In order to prove that the entire function of the heart is replaced by the mechanical apparatus it is necessary to show that none of the blood circulating through the pulmonary circuit or systemic circuit is ejected by the right ventricle or left ventricle, respectively. The main pulmonary artery is ligated during the period of pump activity proving that all blood reaches the lungs via the right pump. Occlusion of the main pulmonary artery does not cause dilatation of the right heart during the pump activity. During the period of occlusion

of the main pulmonary artery the stroke volumes of the left and right pumps are identical. Since both pumps are operated at the same rate, both pumps emit equal minute volumes. Long strips of intra-aortic pulse wave tracings are taken using the electromanometer. These records over a period of 2 to 3 minutes show only pulse wave forms characteristic of pump activity. No pulse wave forms characteristic of left ventricular ejection of blood are present. During pump activity left ventriculotomy exposes an essentially bloodless ventricular cavity. All these findings go to indicate that during pump activity the animal's heart does not function as a pump although it beats and are evidences of complete replacement of cardiac activity by the pumps.

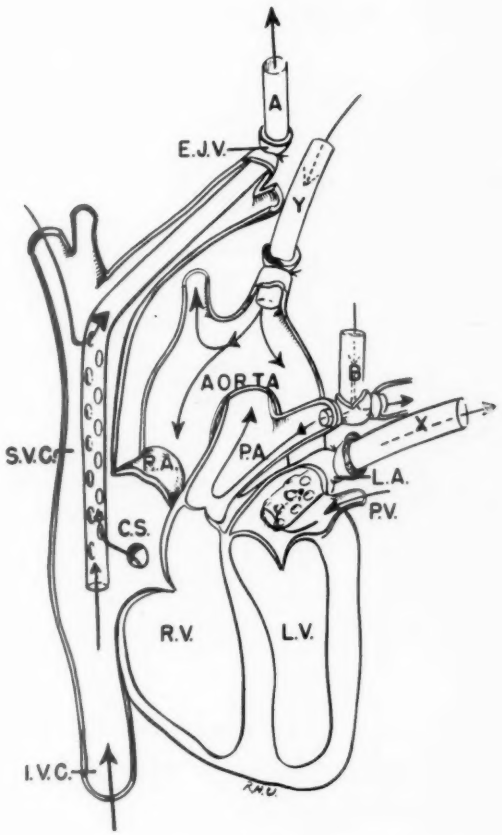

Fig. 6.—Schematic diagram of cardiac cannulations. *A*–caval cannula, *B*–left pulmonary artery cannula, *X*–left atrial cannula, *Y*–left brachial artery cannula, *C.S.*–opening of coronary sinus, *E.J.V.*–left external jugular vein, *I.V.C.*–inferior vena cava, *L.A.*–left auricular appendage, *L.V.*–left ventricle, *P.A.*–main pulmonary artery, *P.V.*–pulmonary vein, *R.A.*–right auricular appendage, *R.V.*–right ventricle, *S.V.C.*–superior vena cava. (Courtesy of W. B. Saunders Company.)

When the function of only one side of the heart is replaced the other side of the heart continues to function in normal fashion. During functional right-sided heart replacement the right ventricle decreases in size while the left ventricle is of normal size and contour and continues to eject blood into the aorta. Conversely when the left heart is replaced by the pump the left

ventricle decreases in size while the right heart continues to pump blood into the pulmonary circuit in normal fashion. During simultaneous replacement of the function of both sides of the heart both ventricles decrease in size sufficiently to admit nearly the entire hand of the operator between the pericardium and the heart. During functional replacement of the entire heart the latter decreases by half in size.

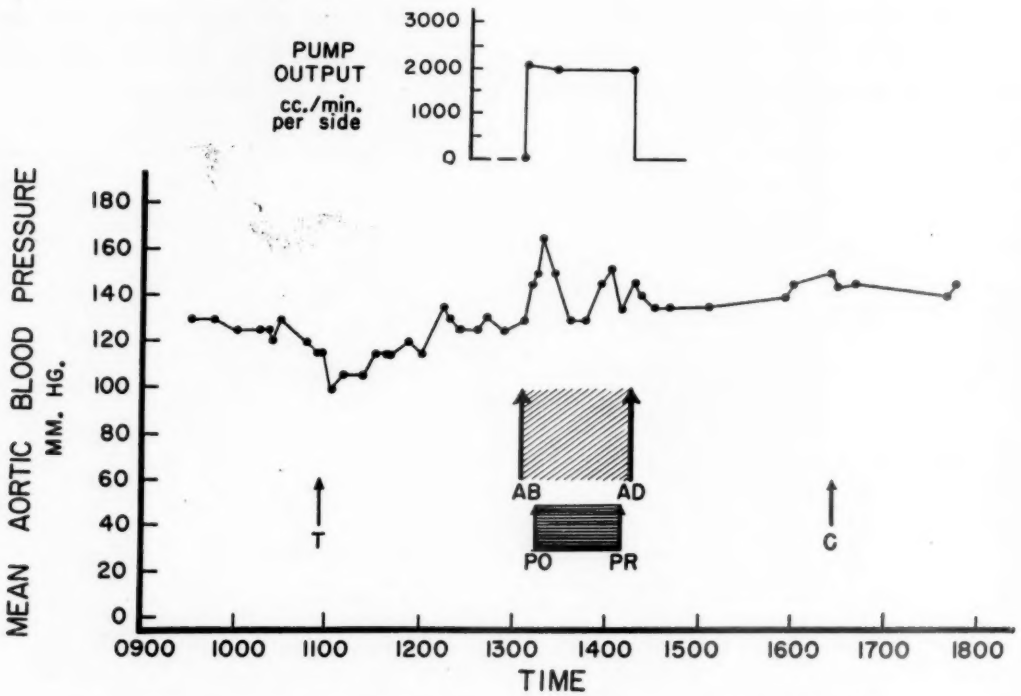

Fig. 7.—Graph of mean aortic blood pressure during functional replacement of both sides of the heart. *T*–time of thoracotomy, *C*–time of chest closure. Cross-hatched area between *AB* and *AD* represents the period of time that the entire heart was completely replaced by the pump. The smaller cross-hatched area between *PO* and *PR* represents the period that the main pulmonary artery was completely occluded. The insert graph above depicts the minute volume output which averaged 2,000 c.c. per minute per side.

Maintenance of Systemic Blood Pressure During Functional Replacement of the Heart

During artificial maintenance of the pulmonary and systemic circulations normal aortic blood pressure can be maintained without difficulty. Fig. 7 is a graph of the mean aortic blood pressure plotted against time from the protocol of a bilateral functional replacement experiment. The blood pressures were obtained via a polyethelene cannula threaded into the abdominal aorta through the right femoral artery. A mercury manometer was used to record blood pressure. Aside from the 30 mm. drop in blood pressure incident to thoracotomy the mean aortic blood pressure remained above 120 mm. Hg. throughout the experiement. The rise in mean aortic blood pressure which occurred about five minutes after the beginning of pump activity shows the effect of rapid infusion of 100 c.c. of blood directly into the aorta. The two

smaller rises near the end of the period of pump activity were the result of rapid intra-aortic transfusions of 50 c.c. of blood. When the dog was placed in his cage the blood pressure was 130 mm. Hg.

Pulse Wave Forms of Pump

During complete functional replacement of both sides of the heart combined with occlusion of the main pulmonary artery, electromanometric pressure tracings were taken from within the abdominal aorta via a polyethelene catheter inserted through the femoral artery. Tracings were also taken from within the main pulmonary artery at the site of its bifurcation via a 25 gauge needle. Fig. 8 is a photograph of the pulse wave forms taken before, during, and after pump activity. All three intra-aortic tracings exhibit similar systolic and

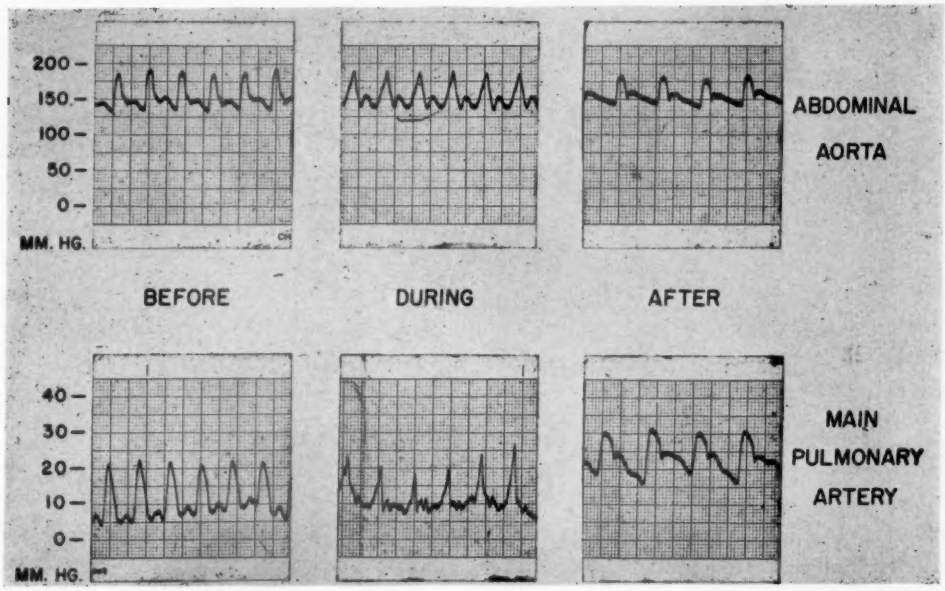

Fig. 8.—Pulse wave tracings recorded with an electromanometer during functional replacement of both sides of the heart combined with ligation of the main pulmonary artery

diastolic values. The pulse pressures are reasonably similar. The main differences in pulse wave forms during pump activity lie in the type of systolic rise emitted by the pump. This consists of a straight systolic rise. Between the pulses there is a secondary wave probably due to aortic rebound. Also notable is the absence of the dicrotic notch during pump activity, probably due to constant closure of the aortic valve. During the period of pump activity pulses within the main pulmonary artery are somewhat similar although recognizably different from those taken when the dog's heart was functioning. The pump pulse wave forms appear more spiking. After cessation of pump activity the pulse wave forms within the main pulmonary artery demonstrate higher pressure with pulse wave forms at a slower rate. These, however, are considered to be within the limits of normal variation for dogs.

Electrocardiographic Tracings

Electrocardiographic tracings were taken during complete functional replacement of both sides of the heart. Tracings were recorded at various times throughout the procedure. In successful replacements an occasional supraventricular premature beat was the only variation from the normal sinoauricular

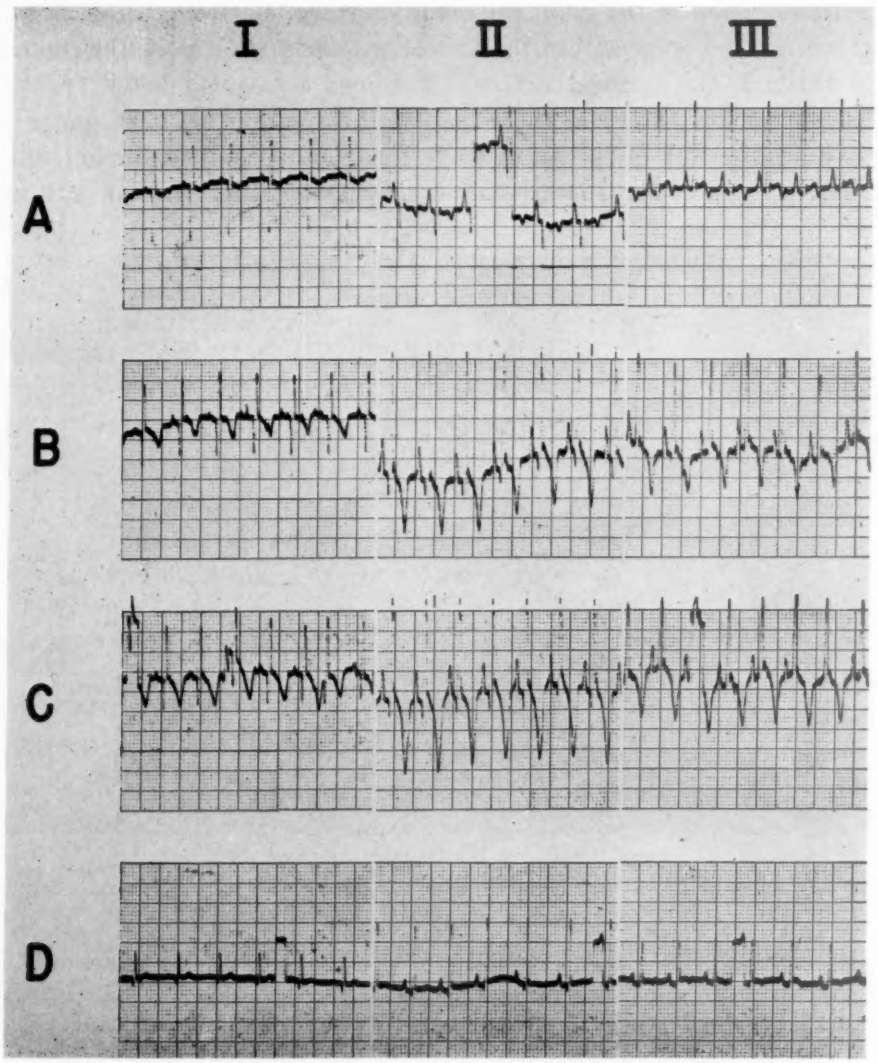

Fig. 9.—Electrocardiographic tracings during bilateral cardiac replacement. *I*, *II*, and *III* refer to the standard limb leads. Tracings *A* are controls taken prior to thoracotomy. Tracings *B* were taken with the left thorax open immediately prior to initiation of pump activity. The tracings of *C* were recorded after 35 minutes of pump activity (the main pulmonary artery had been ligated for 26 minutes). Tracings *D* were recorded on the seventh day after operation.

rhythm. The most striking changes in the tracings during the period of pump activity consisted of increased voltages of P and R waves with inverted and very deep T waves in all three limb leads. These changes can be seen in Fig. 9. They were considered to be due entirely to changes in the electrical axis of

the heart during pump activity. The exact cause of these changes in the electrical axis of the heart during pump activity is not known at present. They are temporary and revert to normal postoperatively.

CHANGES IN THE BLOOD DURING PUMP ACTIVITY

Blood studies were performed at varying intervals during the procedure of circulating dog's blood through the isolated pump apparatus and also during experiments where the pumps were used to maintain the dog's circulation artificially.

Control Experiments

The minute volume of each pump during the control study, when blood was not circulating through the dog but only in the pumps, varied from 4,000 to 5,000 c.c. The pumps were prepared in the same fashion as for use in a replacement procedure. The blood for priming the pump was drawn from a single donor. Test samples were withdrawn from the donor animal by venipuncture, from the donor blood after it was collected in a bottle, and from the pump after it was primed and at intervals up to three hours of pump activity.

Cellular Elements of the Blood.—The hematocrit values remained stationary at about 38 per cent during the three hours of pump activity. The values for free plasma hemoglobin levels rose somewhat during the three hours but remained below plasma levels, in dogs, that were associated with hemoglobin excretion in the urine. The donor dog control value was 1.6 mg. per 100 c.c. of plasma. The mere manipulations of blood collection and priming the pump caused the level of plasma hemoglobin to rise to 17.6 mg. per 100 c.c. During pump activity the rise was linear and was found to be 56 mg. per 100 c.c. of plasma after 3 hours of blood pumping at the rate of 9,000 c.c. per minute. These are probably safe levels for human subjects. The white blood cell count remained consistently about 7,000 per cubic centimeter throughout the three-hour period. The differential count did not change. The platelets were counted in a calibrated chamber using the supernatant plasma of an oxalated sample of blood which was allowed to settle within siliconized tubes. The count of the donor dog was 265,000 per cubic millimeter. Simple collection of the donor blood in a bottle lowered the level to 152,000 per cubic millimeter; priming of the pump further reduced the level to 67,000 per cubic millimeter. Samples taken after 15, 60, and 120 minutes of pump activity showed levels of about 10 per cent of the donor dog control.

Bacteriologic Cultures.—The pumps used in the present experiments could not be sterilized by autoclaving. The whole apparatus was filled with a 1:1000 aqueous solution of Zephiran for 18 hours before its use. Samples for culture were withdrawn from the output lead of the pump during the control experiments. In 24 hours there was no growth on blood agar streak plates, broth, or agar pour plates in any sample. In 48 hours there was sparse growth of *Pseudomonas aeruginosa* in all samples taken from the pump. The blood of the donor dog before and after collection showed no growth. The pour plates

showed 2 to 11 colonies per cubic centimeter in the samples taken at intervals between 15 and 180 minutes of pump activity. The Pseudomonas were not laboratory contaminants, but probably pump contaminants from the stopcocks in the air traps. These stopcocks are the main source of contamination in the pump. When the samples for culture were withdrawn via the stopcocks over 2,000 colonies of *Pseudomonas aeruginosa* per cubic centimeter were observed in the pour plates after 48 hours' incubation. Substitution of the stopcocks with short segments of rubber tubing that can be clamped should provide a safer mechanism.

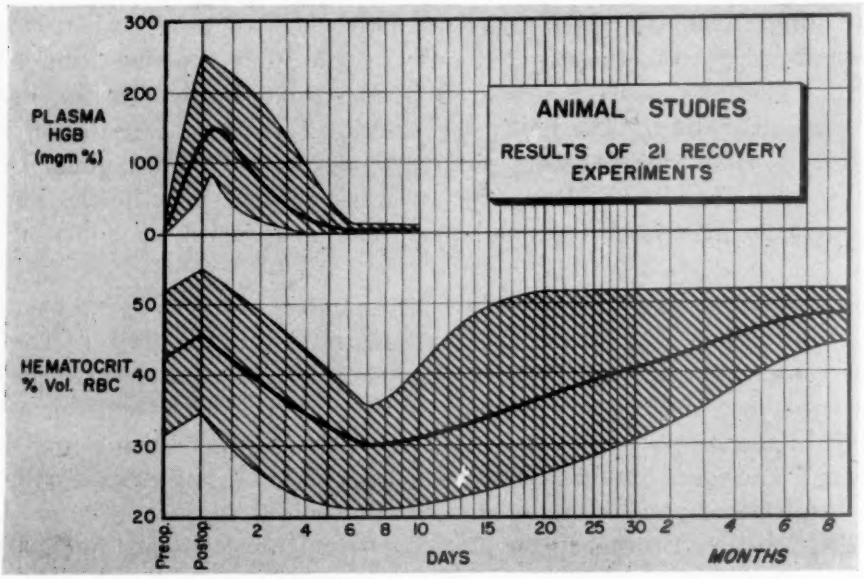

Fig. 10.—Graph of free plasma hemoglobin levels and hematocrit determinations following functional replacement of the heart. The heavy black lines indicate the average values while the cross-hatched areas represent the range of variation of the values. In spite of adequate urinary output the plasma hemoglobin levels remained elevated for 5 days after operation suggesting continued hemolysis after functional replacement of the heart had been discontinued. The progressive drop in the hematocrit during the first 7 postoperative days supports this view. The hematocrit had returned to normal after 1 month of regular laboratory diet.

Animal Studies

Hematocrit.—The preoperative hematocrit values in the group of dogs used in these experiments varied between 32 and 52 per cent. During the operative procedure the hematocrit was maintained adequately by transfusions of whole blood. Immediate postoperative values paralleled the control values. In twenty-one animals which survived after pump replacement of the heart for 1 hour or more a fall in the hematocrit to an average of 32 per cent was noted in the first week after the experiment. At the end of 2 to 4 weeks, the hematocrit regained or surpassed the preoperative value (Fig. 10).

Plasma Hemoglobin.—In the dogs used, the upper normal limit of free plasma hemoglobin was taken at 15 mg. per 100 c.c. of plasma. The amount of hemolysis due to pump activity in the control studies using two pumps in parallel for 3 hours was found to total 56 mg. of free hemoglobin per 100 c.c.

of plasma. Yet, after 1 to 2 hours of artificial maintenance of both circulations the levels varied from 50 to 255 mg. per 100 c.c. of plasma (average 136). During the first 5 postoperative days, the plasma hemoglobin levels remained elevated, often exceeding the immediate postoperative level. While the hematocrit was falling, the plasma hemoglobin remained elevated in the face of an adequate urinary excretion. It would seem from these data that the average life of the red blood corpuscles used in perfusing the animal was shortened as a result of mechanical trauma. During the first postoperative week the blood volume remained constant. The hematocrit drop during this period, therefore, was not related to a dilution mechanism but to an actual loss of circulating red blood corpuscles. In human subjects cross-matching is routine and the red blood corpuscles are more resistant to mechanical trauma. The free plasma hemoglobin levels, therefore, might remain well below the renal threshold level during pump replacement of the human heart.

Platelet Counts.—Four counts of platelets were taken during replacement. One sample drawn after 103 minutes of artificial maintenance of both the systemic and pulmonary circulations contained 130,000 platelets per cubic millimeter of blood (adequate level, although only 50 per cent of normal). The same counting method was used in the pump control tests in which after 90 minutes of pump activity only 20,000 platelets per cubic millimeter (10 per cent of normal) were found. This suggests that the animal can maintain adequate platelet levels in spite of removal of the same from the circulation by destruction and/or agglutination.

Clotting Time.—The dosage of heparin administered to the experimental animals prolonged the clotting time to as long as 24 hours. After artificial maintenance of the circulation was discontinued and the animal's own heart allowed to regain its function enough protamine was given to reduce the clotting time to normal (11 minutes or less by the three-tube method). In spite of a normal clotting time some animals seemed to be left within the first 12 postoperative hours with a qualitatively weaker clot as determined by direct inspection of a clotted sample. During thoracotomy in the heparinized animal a significant oozing of blood occurred. This oozing was largely abolished after the administration of protamine. All animals could be restored to a normal clotting time by adjustment of the protamine dosage. Once the clotting time was restored to normal it was stable; that is, there was no "negative phase" of delayed clotting time caused by the protamine-heparin combination. All clotting times observed during the first 72 postoperative hours were found to be normal. The intrathoracic hemostasis had to be especially rigid. All dissections were carried out before heparin was administered. Ligation of cut pericardial vessels and repleuralization of denuded areas were important in controlling ooze.

Chemical Studies.—Preliminary gas analysis studies showed no significant deviation from normal in the oxygen content or carbon dioxide content of the blood during artificial maintenance of the circulation. When the function of both sides of the heart was replaced there was a striking contrast in the color of the blood circulated through the two pumps.

Blood volume determinations conducted directly before and directly after the period of artificial maintenance of the circulation showed no great changes in total blood volume or total red-cell mass. The Evans blue dye method was used. Determinations made during pump activity were absurdly high even after correction for the volume of blood in the pumps; this effect was probably the result of adsorption of the dye by the rubber tubing in the pump apparatus.

RESULTS OF FUNCTIONAL CARDIAC REPLACEMENT BY PUMPS

The 68 experiments included in this report were done in the period from July, 1949, to October, 1950. Usually, large dogs were used although they varied from 22 pounds to 58 pounds with an average weight of 43.8 pounds. The experiments are divided for the purpose of this report into three groups: preliminary, physiologic, and recovery experiments.

Preliminary Experiments

This group includes, among others, the first 26 experiments which were conducted without using aseptic surgical technique. Fundamental problems concerned with pump development and cannulation procedure were solved during these experiments. Early experiments in this group were concerned with "extinction" experiments; that is, functional replacement of the heart was continued for prolonged periods of time and the animals were observed without attempt at supportive treatment. For example, in one experiment of this group complete functional replacement of the left heart was maintained for a period of 7½ hours after which time the animal succumbed to the effects of hypotension. As the procedure of cannulation was developed, ventriculotomy on the left was done to demonstrate that the replacement of the left side was complete and that the left ventricle was essentially bloodless during the period of pump activity.

Physiologic Experiments

In these experiments, specific details as regards perfection of technique and special studies such as electrocardiographic tracings and electromanometric pressure tracings at various sites were done without particular attempt at recovery of the experimental animal. During other experiments, observations of the efficacy of a nonpulsatile flow in maintenance of arterial blood pressure were made. Data concerned with the effect of pulse rate on arterial tension were gathered. These observations are recorded below.

The Effect of a Nonpulsatile Flow on Arterial Blood Pressure.—A basic question of artificial maintenance of the circulation is whether or not a pulsatile flow is necessary. From the work of Gibbon and associates[5] and Kantrowitz and Kantrowitz,[12] it would seem that essentially nonpulsatile flows are adequate for artificial maintenance of the circulation for short periods of time. In an attempt to answer this question a small number of experiments were performed on animals using our apparatus, which emits a pulsatile flow, in series with a "depulsating" apparatus situated between the pump and the arterial cannula in the animal.

Fig. 11 is a diagram of the "depulsating" apparatus. It consists of a rubber membrane of Gooch tubing stretched within a pump chamber. The sidearm of the pump chamber is connected to a Fenwal bottle of 1,500 c.c. capacity. The Fenwal bottle is fitted with a mercury manometer for measure-

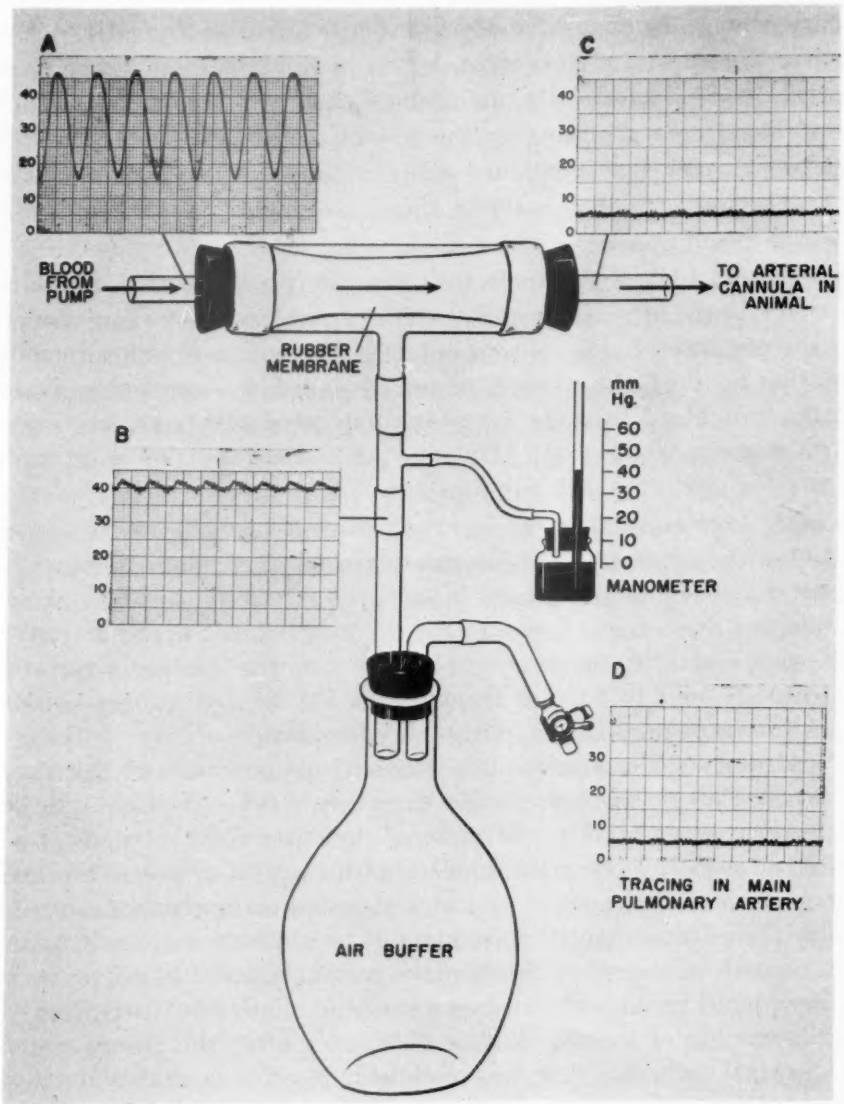

Fig. 11.—Diagram of the "depulsating" apparatus illustrating the marked dampening of the pump pulse (shown in tracing *A*) after passing through the apparatus. The pressures illustrated are for use in nonpulsatile perfusion of the lesser circulation. The same apparatus has been used for nonpulsatile perfusion of the systemic circulation at higher pressures.

ment of the pressure within it, and with a three-way stopcock for the insertion of air. Sufficient air is inserted into the mechanism to cause a pressure around the rubber membrane of the order of the mean arterial blood pressure of the circulation to be perfused. Under these conditions the pulse pressure distal to the "depulsator" approaches zero, and the blood flow through the arterial

cannula into the animal is essentially a steady flow. With this system the minute volume can be computed by multiplying the rate of the pump by the stroke volume of the pump which emits a pulsatile flow *into the "depulsator."*

Three experiments were conducted using this system. In two of these experiments the function of the left heart was replaced, while the function of the right heart was replaced in the third experiment. In the latter experiment functional replacement of the right heart was carried out for 125 minutes. Blood pressure was adequately maintained and transfusion of only a small amount of blood corresponding to the operative loss was necessary. Electromanometric pressure tracings taken from within the main pulmonary artery during the period of pump activity showed complete absence of pulse wave forms in the tracings with a mean pulmonary artery pressure of 8 mm. Hg. This pressure did not vary more than 2 mm. during the period of the tracings. During the 2 hours of pump activity the eye reflexes of the dog remained intact and the respiratory reflexes were intact. The venous pressure remained normal and the color of the animal remained excellent, suggesting that a nonpulsatile flow of blood into the lungs is compatible with complete oxygenation of the pu'monary blood flow. During this procedure the main pulmonary artery was occluded for 101 minutes.

In both experiments in which the systemic circulation was artificially maintained with a nonpulsatile flow for a period of 2 hours it was noted that a very large amount of transfused blood, approximately 1,500 c.c., was needed to maintain the dog's blood pressure for the first hour of pump activity. After 1 hour of pump activity using a nonpulsatile flow the lowered arterial pressure did not respond well to further transfusions but seemed quite sensitive to the action of intravenous Neo-synephrine Hydrochloride. One of these animals died of pulmonary edema after 2½ hours of replacement of the function of the left ventricle by the pump, while the other recovered from anesthesia and died 12 hours postoperatively. Autopsy of the latter revealed signs of a massive myocardial infarct involving the whole anterior aspect of the left ventricle and anterior portion of the septum. Both of these animals were considered to have died from the effects of overtransfusion. The state of overtransfusion, it was felt, was caused by the effort to maintain normal arterial blood pressure in the face of peripheral pooling of blood as a result of diminished peripheral vascular tone in the absence of a pulsatile flow of blood. After the pumps were stopped and the normal pulsatile flow was regained, blood was redistributed with resultant overfilling of the vascular tree. The syndrome of decay of peripheral vasomotor tone has not been observed in those experiments in which a pulsatile type of flow was used to maintain the systemic circulation artificially for as long as 2½ hours. For periods of 2 hours a nonpulsatile flow is adequate to artificially maintain the pulmonary circulation. The systemic circulation can be adequately maintained with nonpulsatile flow for periods of time up to 1 hour but beyond this period of time there is a decided loss of peripheral vasomotor tone resulting in hypotension that responds poorly to transfusions. An extracorporeal heart pump that delivers a pulsatile type of flow seems preferable

to a pump mechanism which delivers a nonpulsatile type of flow. It appears that the pulse has a definite physiologic role in the maintenance of peripheral vasomotor tone and, therefore, of arterial blood pressure.

The Effect of Pump Rate on Arterial Blood Pressure.—In order to evaluate the significance of pulse rate upon the maintenance of aortic blood pressure a series of three experiments was done. All three of the animals were subjected to simultaneous replacement of the function of both sides of the heart for periods of time from 96 to 109 minutes. The main pulmonary artery was occluded during the period of pump activity. The rate of the pump was varied from 75 to 185 strokes per minute during 20-minute periods of time and the intra-aortic pressure was recorded using an electromanometer. It was found that the mean aortic blood pressure remained within normal limits independent of rate of stroke (pulse rate of pump). As the stroke rate was decreased the pulse pressure increased with an accompanying increase in systolic pressure and decrease in diastolic pressure but with a constant mean pressure. When the stroke rate was increased there was decrease of the pulse and systolic pressures, increase in the diastolic pressure, but again a constant mean aortic blood pressure. Fig. 12 is a photograph of a group of electromanometric pulse wave tracings taken during one of these experiments. The physiologic implications to be made from the observations recorded in Fig. 12 indicate that provided the minute volume of pump output remains constant the stroke rate may be varied 50 per cent slower or faster than the dog's normal rate without significant change in mean aortic blood pressure.

Recovery Experiments

The aim of the 28 experiments included in this group was the clinical recovery of the experimental animal after functional replacement of one or both sides of the heart. In nine out of eleven consecutive unilateral left or right heart pump replacement experiments the animals recovered. Twelve dogs out of seventeen subjected to pump replacement of both sides of the heart recovered. The results of these experiments constitute the present index of safety for the replacement techniques described. It should be pointed out at this time that a rather high infection rate occurred in the animals that recovered. This was a result of inadequate attention to the problem of bacterial contamination both from the viewpoint of the operative procedure and of sterilization of the pump. The pump described is constructed of Lucite, and as such, cannot be sterilized by autoclave. This necessitates chemical sterilization of the pump which, as previously pointed out, is presently inadequate. Therefore, animals who exhibited their normal preoperative behavior postoperatively, and gained steadily in activity while exhibiting no symptoms referable to artificial maintenance of the circulation but who died as a direct result of late postoperative infection were considered to have recovered. All animals in this series were autopsied. Those animals that succumbed with late postoperative infection were shown at necropsy to have died from the effects of infection.

In the 7 experiments out of the total 28 in which the animals failed to survive heart replacement, technical errors were the principal causes of death. One animal died as a result of air embolism through the left atrium. Prolonged hypotension, hemorrhage, and overtransfusion were other causes of

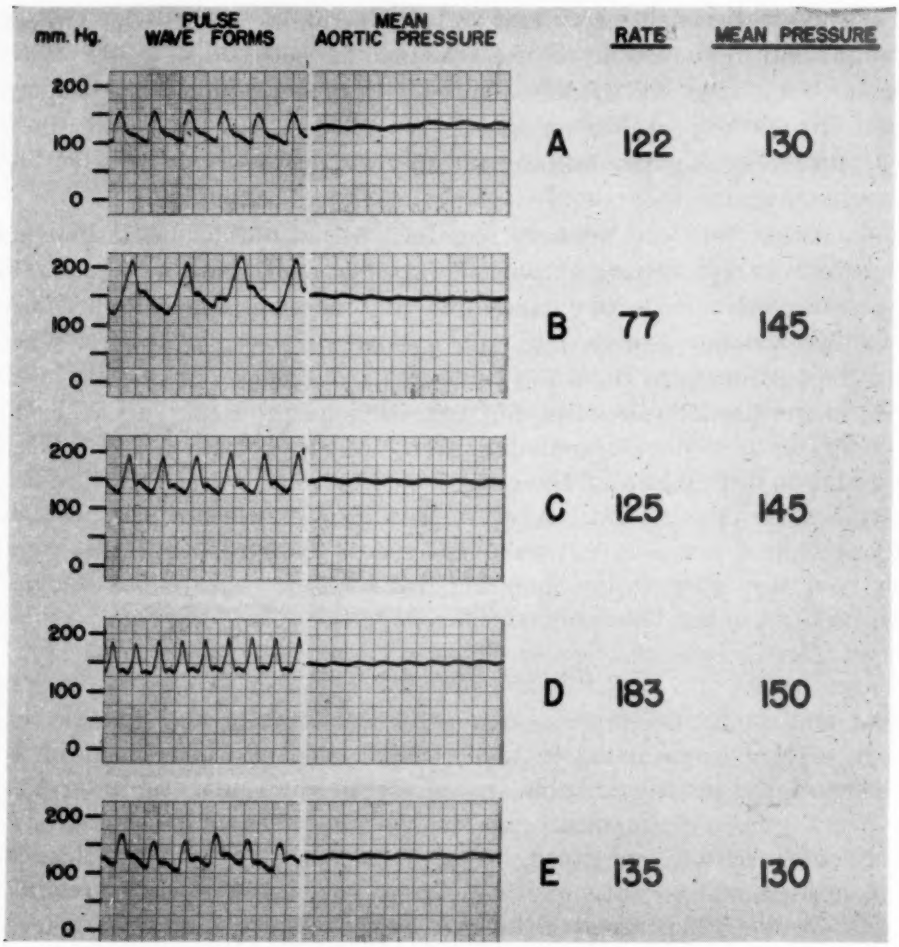

Fig. 12.—Electromanometric tracings showing the effect of pulse rate on aortic blood pressure. Each tracing consists of a short strip of pulse wave forms and mean pressure recordings. *A*, is a control record prior to pump activity. The mean pressure is 130 mm. Hg with a heart rate of 132 beats per minute. The pulse wave forms are characteristic of left ventricular activity in the dog. Tracings *B*, *C*, and *D* are recordings taken during complete functional replacement of the entire heart accompanied by occlusion of the main pulmonary artery. Note the differences in pulse wave forms during the period of pump activity. In tracing *B* the pump rate is 77 strokes per minute. The mean aortic blood pressure hovers about 145 mm. Hg. In tracing *C* the pump rate was set at 125 strokes per minute and the mean aortic blood pressure is approximately 145 mm. Hg. In tracing *D* the pump rate was set at 183 strokes per minute. The mean aortic blood pressure at this pump rate is 150 mm. Hg. Tracing *E* is a control tracing taken four hours after replacement of cardiac function was discontinued. The pulse wave forms again are characteristic of left ventricular activity. The heart rate is 135 beats per minute and the mean aortic blood pressure is 130 mm. Hg.

failure. There were 9 late postoperative deaths from empyema and generalized infection among the 21 dogs who survived heart replacement. These animals died from 5 to 28 days after operation. A tenth animal that recovered died of cerebral distemper on the nineteenth postoperative day.

Functional Replacement of the Left Heart.—There were 7 consecutive attempts at functional replacement of the left heart. With the exception of the first experiment in this series all were conducted using aseptic surgical technique. In 6 out of these 7 experiments the entire systemic circulation was artificially maintained by the pump for a period of 1 hour. The single failure in this group occurred as the direct result of a technical error before artificial maintenance of the circulation could be carried out. The systemic circulation of 6 of the animals was successfully maintained by the pump. All recovered from the procedure. Two of the animals that recovered were sacrificed 3 months and 5 months after operation. The post-mortem examinations of these 2 animals were unremarkable with the exception of the operative scars. The remaining 3 animals that recovered did well in the immediate postoperative period but died 5, 6, and 17 days postoperatively from infection. Necropsy of these 3 showed that these animals died as a direct result of infection. The sixth animal is alive with normal behavior 19 months after operation. The recovery rate in this series of experiments is 6 out of 7 or 86 per cent.

Functional Replacement of the Right Heart.—There were 4 consecutive experiments in which the right heart was artificially maintained for 1 hour or more. The first right heart replacement attempted was a failure because of a prolonged hypotension. During the remaining 3 experiments functional replacement of the right heart was carried on for a period of 60 to 102 minutes with adequate maintenance of blood pressure and with recovery of the experimental animal. None of these 3 animals developed postoperative infection. They were sacrificed 2 months, 4 months, and 4 months after operation, respectively. The recovery rate in this small series is 3 out of 4.

Functional Replacement of Both Sides of the Heart.—Seventeen attempts at simultaneous artificial maintenance of the systemic and pulmonary circulations were done in 2 consecutive groups. Twelve out of the seventeen experimental animals recovered from the procedure. During the period of functional replacement of the heart in these 12 animals the main pulmonary artery had been completely occluded with umbilical tape for periods of time varying from 60 to 109 minutes. Six of these twelve animals died of late postoperative infection and 4 were sacrificed for further study at 4½, 5½, 5½, and 6 months after operation, respectively. Two animals of this group are being observed at present. Both are in healthy condition and are at the time of this writing 10 months and 16 months postoperative. Post-mortem examinations of some of the sacrificed animals showed evidences of small healed mural thrombi at the junction of the vena cava and right atrium. In 2 of the animals that died as result of infection, vegatative thrombi were found at the junction of the superior vena cava and right atrium. In one of these animals there was evidence of septic embolization to the lung. The animals that died of infection consistently succumbed to compression atelectasis of both lungs as a result of empyema fluid pressing on lung tissue. In dogs, the anterior mediastinum is flimsy or nonexistent. Empyema is, therefore, a bilateral and fatal disease in dogs if untreated. Post-mortem examination of the 10 animals that recovered

and were sacrificed or that died from infection showed all cannulation sites to be intact with no evidence of leakage. The repair of the left pulmonary artery was healed in all of these animals with no decrease in the size of the lumen nor evidence of thrombosis at the cannulation site. No animal in this group of experiments exhibited any central nervous system signs or symptoms referable to the procedure of artificial maintenance of the circulation. Each dog that recovered regained his preoperative behavior pattern and during the first week exhibited his normal preoperative activity. About half of the animals that recovered could rise spontaneously and walk with a gait that was normal except for a slight limp in the left foreleg 12 hours postoperatively. The remainder regained a normal gait within the first postoperative week. All of the animals were eating their normal laboratory diet within 3 or 4 days after operation. An occasional dog could leap up upon a three-foot laboratory table on the third postoperative day. Four animals showed a transient Horner's syndrome on the left side probably due to edema of the vagosympathetic ganglion as a result of handling at the time of the brachial artery cannulation. In those animals now being observed no untoward signs or symptoms are exhibited. The recovery rate for attempts at functional replacement of the entire heart combined with occlusion of the main pulmonary artery is 12 out of 17 or approximately 70 per cent. The combined recovery rate for attempts at unilateral heart replacement and bilateral heart replacement reported in these results is 21 out of 28 or 75 per cent. Further perfection of the technique of functional cardiac replacement by pumps can be made. The construction of an autoclavable pump should help reduce infection and late deaths. The results of the recovery experiments are summarized in Table I.

TABLE I

PART REPLACED	NO. EXPERIMENTS	NO. RECOVERIES	NO. DIED OF LATE POSTOPERATIVE INFECTION	NO. SURVIVALS	NO. SACRIFICED FOR FURTHER STUDY	LIVING
Left heart	7	6	3	3	2	1
Right heart	4	3	0	3	3	0
Both sides of heart	17	12	7*	5	3	2

*One died from distemper.

SUMMARY

Sixty-eight experiments have been performed in the course of developing an extracorporeal heart pump mechanism for artificial maintenance of the circulation. Descriptions of the pump mechanism, the methods of cannulation, and the techniques of replacing either or both sides of the heart have been given.

The effect of pump activity on the organized elements of the blood has been studied. Physiologic data on arterial blood pressure under varying conditions of pump activity are discussed.

Pump replacement of cardiac function in these experiments has been performed using the animal's own lung as the means of oxygenation of blood.

The data are presented concerning a series of 28 experiments with attempts at recovery of the animals after a period of artificial maintenance of the circulation. Twenty-one (75 per cent) of these animals recovered.

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Surgical History

CONDUCTED BY JOHN R. PAINE, M.D.

COLOSTOMY: HISTORICAL ROLE IN THE SURGERY OF THE COLON AND RECTUM

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SURGICAL intervention for the relief of conditions affecting the colon and rectum forms one of the most fascinating chapters in the history of medicine. For centuries, the victims of obstructing lesions of the colon and rectum, such as carcinoma, were forced to depend upon emetics, purgatives, poultices, and enemas for relief. As the malignancy continued to narrow down the lumen of the bowel, these and all other measures finally failed, and the patient died in agony from his obstruction. Under these circumstances, it became obvious to many physicians that only an external opening in the obstructed dilated bowel, in other words, a colostomy, could relieve these unfortunate individuals. Eventually, courageous and daring surgeons accepted this challenge, established a colostomy, relieved the obstruction, and the surgical treatment of lesions affecting the colon and rectum came into being.

Hundreds of years before the first colostomy was carried out, veterinarians had relieved obstructions in sheep and horses by stabbing the distended abdomen and creating a fecal fistula. Aurelianus Caelius recorded that, 300 years B.C., Praxagoras treated ileus by opening the abdomen, incising the bowel to evacuate it, and then closing it. There is no record as to whether this operative procedure was ever successful.

Littre has been given the credit for having done the first colostomy in 1710 (Fig. 1). Having seen a young infant already dead from obstruction due to maldevelopment of the rectum, he suggested that the infant's life might have been saved by incising the abdomen and either anastomosing the bowel or bringing the proximal end out to the surface as an artificial anus. Although there is no record that he had the opportunity actually to carry out his own suggestion, he deserves the credit for being the first to perceive and to state the answer to this unsolved problem of large bowel obstruction. It was not until 1776, a year so important in the history of this country, that Pillore of Rouen performed the first successful cecostomy for the relief of obstruction caused by carcinoma of the rectum (Fig. 1). Pillore's patient was relieved temporarily and although he died on the twenty-eighth postoperative day, autopsy revealed that the peritonitis which caused his death was due, not to the operative procedure, but to a perforation of the jejunum. The patient had been

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given 2 lb. of mercury preoperatively in a vain attempt to relieve the obstruction, and all the mercury had been retained in a single loop or jejunum, producing erosion and perforation. Antoine Dubois[10] performed Littre's suggested operative procedure for imperforate anus in 1783 (Fig. 1), but the patient died on the tenth postoperative day. Ten years later, in 1793, Duret, of Lyon, carried out the first successful iliac colostomy for this same lesion (Fig. 1). In spite of the misgivings of his colleagues, and because all other measures had failed, he decided to follow the advice of Selsus: "It is better to employ a doubtful remedy than to abandon the patient to certain death." The patient lived for forty-three years, finally dying of an intercurrent infection. Thus, the first modern colostomy was established over one and one-half centuries ago.

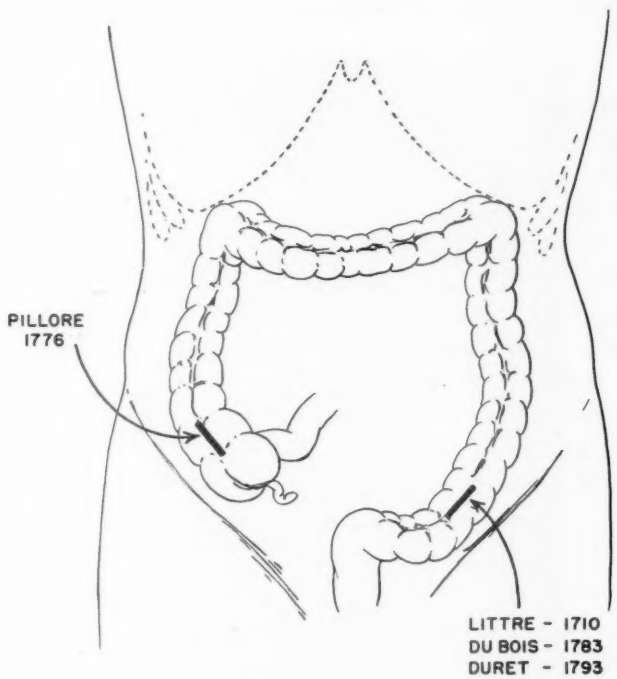

Fig. 1.—Littre, in 1710, conceived the answer to large bowel obstruction. Pillore, in 1776, relieved large bowel obstruction by establishing a cecostomy. Dubois' patient died postoperatively. Duret, in 1793, carried out the first successful iliac colostomy.

In 1795, Daguesceau operated on a patient who had fallen from a wagon, driving a wooden stake into the left lower quadrant of his abdomen, perforating the sigmoid colon. He exteriorized the proximal bowel. The patient recovered and lived for twenty-four years, finally dying at the advanced age of 81. Daguesceau adapted a small leather bag to the opening he had created to receive the fecal contents and thus originated the first colostomy bag. Fine, in 1797, in attempting to relieve obstruction by opening the ileum through a low midline incision, opened instead a low-lying transverse colon, and thus became the first to establish a transverse colostomy. Amussat, an excellent French surgeon, in 1839, was the first to urge that a colostomy be established routinely for obstructing carcinoma of the rectum as a humanitarian measure. It was

Amussat who said, "an artificial anus, it is true, is a grave infirmity but it is not insupportable." These wise words may well be kept in mind today when we consider the frequent use of operative procedures designed to eliminate a colostomy but which, in low-lying rectal lesions particularly, are associated with an increased risk of recurrent carcinoma. In addition to Amussat, Verdans, in 1842, Keyworth, in 1848, and Phillips, in 1850, all made technical advances in right- and left-sided decompressive operative procedures. In 1865, twenty-five years after Clements had carried out the first colostomy in England, Nathaniel Ward urged the adoption of a lumbar colostomy as a routine procedure for rectal carcinoma. Later, Bryant and Ellingham made significant contributions to the surgery of cancer of the rectum, and inguinal colostomy began to displace the less convenient and less satisfactory lumbar colostomy.

COLOSTOMY IN SURGERY OF THE RECTUM

Operative procedures designed to remove cancer of the rectum date back to the proposal of Morgagni early in the eighteenth century, and first attempted by Faget in 1739. These early operative procedures were all variations of a posterior type of proctectomy, and left an uncontrollable anus. The first successful operation was performed by Lisfranc in 1826. This operative procedure was brought to its ultimate development by Kraske who, in 1885, advised posterior proctectomy with removal of the coccyx and part of the sacrum and preservation of the perianal skin and the external sphincter. It was Vincenz Czerny who, in 1883, while attempting one of these posterior resections for carcinoma of the rectum, found he could not bring the growth down. He boldly opened the abdomen, ligated the blood supply to the sigmoid colon and removed the entire segment transperitoneally, bringing the proximal bowel out as a colostomy. This attempt was unsuccessful but the principle of the modern operation for carcinoma of the rectum had been established. The Kraske procedure achieved wide popularity, with the more daring surgeons attempting to achieve better results in the treatment of carcinoma of the rectum by carrying out an inguinal colostomy followed by a second-stage posterior resection. It failed, however, to show any significant reduction in the recurrence rate over the more conservative type of posterior resection and this procedure has now been completely abandoned. It remained for Miles of England (Fig. 2) who, around the turn of the century, developed and perfected his radical one-stage abdominoperineal resection, to establish firmly the modern treatment for carcinoma of the rectum.

This one-stage abdominoperineal resection was slow to be accepted in England, on the Continent, and in the United States. A number of two-stage operations were devised and given an extended trial, including those of W. J. Mayo, Daniel F. Jones, Robert Coffey, Rankin,[15] and others. In an attempt to reduce the mortality associated with the early use of this radical operative procedure, Lahey,[6] in 1930, devised a two-stage abdominoperineal resection (Fig. 3). At the first stage, the proximal end of the divided sigmoid colon was brought out as a permanent colostomy in the left lower quadrant and the distal

end was implanted as a temporary colostomy in the low midline. This permitted the inflammatory reaction associated with these large rectal carcinomas to subside and often permitted resection, at the second stage, of growths which had been considered inoperable at the initial procedure.

Better preparation of the patient, the use of antibiotics and more adequate blood replacement now permit the one-stage Miles abdominoperineal resection to be carried out on almost all patients with cancer of the rectum in whom the growth is resectable. Suggestions have recently been made that this procedure be extended to include all of the inferior mesenteric artery, including the left colic artery. The distal transverse colon or upper descending colon is then used to form the colostomy. Thus, a permanent end colostomy has become an essential part of the modern treatment of cancer of the rectum.

Fig. 2.—W. Ernest Miles, T.D., F.R.C.S., F.R.C.S.I.(Hon.), F.A.C.S.(Hon.), 1869-1947. Miles established the modern operation for cancer of the rectum. It is as a part of his abdominoperineal resection that colostomy is most frequently performed at the present time.

The modern conception of adequate treatment for these patients involves not only carrying out a radical removal of their growth and the establishment of a satisfactory colostomy, but also should include teaching them so to regulate their colostomy by diet and irrigation that bowel movements occur only at specified times. This means not only that life becomes supportable, as Amussat stated in 1839, but also means that the colostomy bag can be eliminated, and these patients permitted to resume their normal social and economic activity.

Patients who require a permanent colostomy need the personal care and understanding consideration of their surgeon to overcome the natural concern

associated with their new situation. They need it particularly during their postoperative period and many will need it for some time to come in order to acquire confidence in their ability to carry on as before.

COLOSTOMY IN SURGERY OF THE COLON

The young surgeon acquiring his training today might well think that the subject of colostomy has little to do with the modern treatment of obstructing lesions of the colon, such as malignant disease. Yet the establishment of

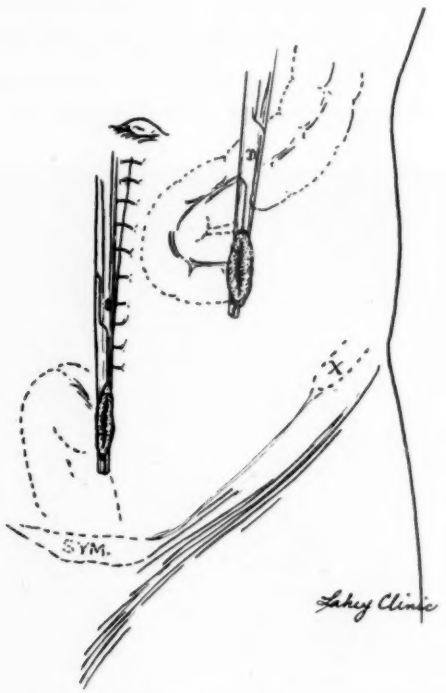

Fig. 3.—The midline colostomy is the temporary colostomy and is removed at the time of the second stage when the rectum is removed by an abdominoperineal resection (Lahey two-stage resection).

a temporary colostomy has had a long and intimate association with the treatment of lesions of the colon such as malignancy, diverticulitis, and segmental obstructive colitis. Billroth, in 1879, did a resection of the sigmoid colon, closing the distal end and bringing the proximal end out as a colostomy. In the same year, Shede in resecting a lesion of the colon found it impossible to approximate the two ends and was forced to exteriorize both the proximal and distal bowel. Thus, unintentionally, Shede established the principle of the graded resection for lesions of the colon. Marshall, in 1882, carried out the operation which Billroth had described and established a colostomy through a stab wound in the iliac fossa.

In 1892, Murphy published his work on the Murphy button, which represented a marked advance in surgery of the small and large bowel. The mortality following resection and anastomosis of the colon remained high, and the same year, Oscar Bloch of Norway, discouraged by mortality rates of 47 to 59 per

cent, suggested that carcinoma of the sigmoid be exteriorized and resected outside the abdomen. He successfully carried out this procedure, placing a tube in the proximal loop. This was later modified by Hochenegg to include more of the regional lymph nodes.

In 1895, Paul,[9, 13] of Liverpool, England, apparently unaware of the work of Bloch, reported 7 cases of resection of the colon. Speaking with disarming candor he described his 7 cases as follows: "3 patients died outright, one died of a second operation to restore continuity and the sum total of the existence of the remaining 3 survivors was nothing to boast of." After attempting to perform an immediate anastomosis by invagination over a bone tube and losing

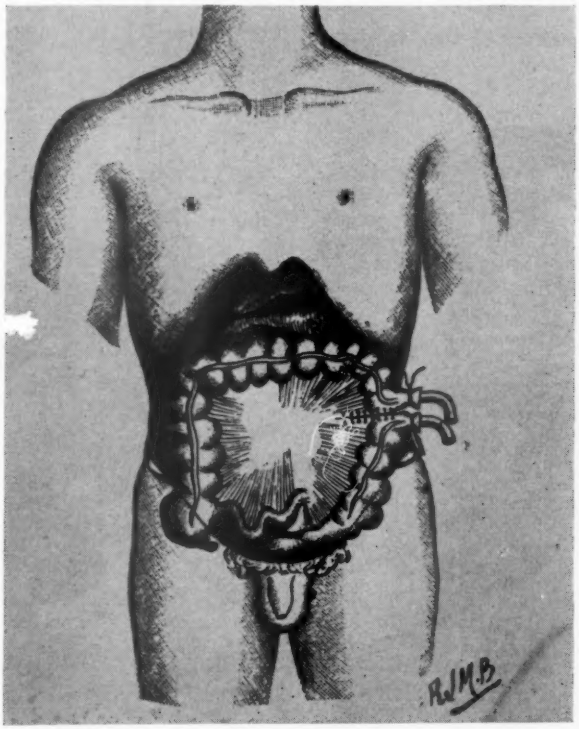

Fig. 4.—Paul's illustration of his operative procedure. We might consider his "spur" to be a little short but otherwise this drawing, made in 1895, could be accepted today as an illustration of the exteriorization procedure.

the first 3 patients, he decided to resect the tumor, exteriorize the proximal and distal bowel and place a glass drainage tube in each (Fig. 4). This was an advance over the suggestion of Bloch in that he excised the exteriorized portion at the time of the first operative procedure, thus avoiding the very real danger of implantation of the carcinoma in the operative wound. His fourth patient lived for two years and died without recurrence. Paul was impressed with the safety of his method. He carried out the same procedure on a fifth patient who also did well, but one month later the patient died from peritonitis four days after Paul had restored intestinal continuity by direct anastomosis. It was then that he stated, "There remained, however, to be tried, an old plan of restoring continuity by Dupuytren's enterotome to which very little risk is

attached. If such a method could be performed successfully when the spur is formed by nature, how much more ought it to be so when a spur was deliberately constructed with the object of being subsequently safely removed." He then carried out this method of two-stage resection and closure successfully. He concluded his paper with the following remarkable statement: "With the patient in good condition, his abdomen not distended, the tumor small and the proximal end of the bowel not greatly hypertrophied, I would immediately restore continuity following resection by use of the Murphy button but I would resort to this method (exteriorization) when these conditions do not prevail." By the substitution of "primary anastomosis" for "Murphy button," this statement made fifty-seven years ago might well be applied to the modern treatment of carcinoma of the colon.

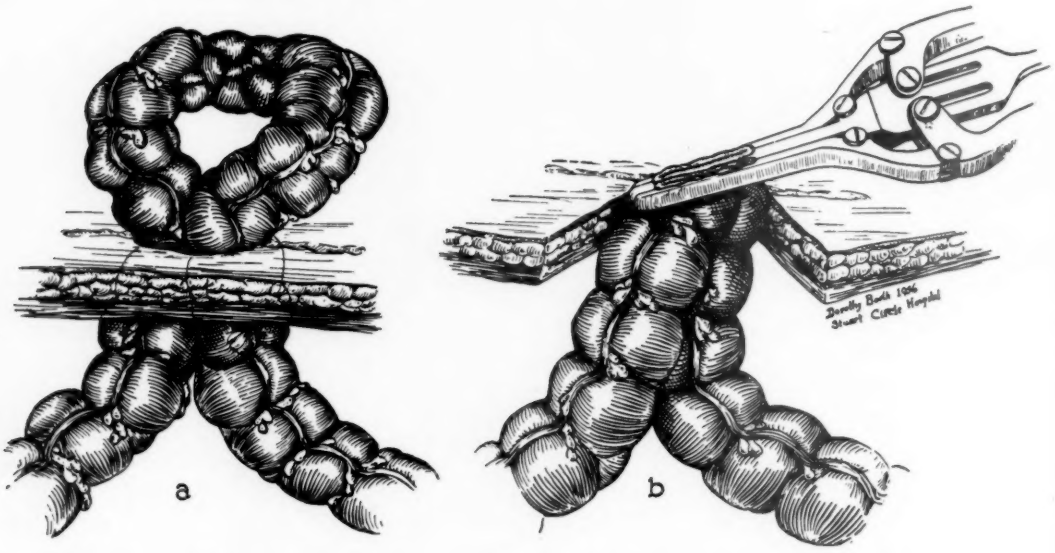

Fig. 5.—*a*, The original Mikulicz procedure. The segment of sigmoid colon containing the growth was exteriorized. Later the exteriorized segment was removed.

b, Obstructive resection by Rankin. Although the double barreled colostomy is not unlike that of Paul or Mikulicz, the resection of the adjacent mesentery is far more extensive than that carried out by these earlier surgeons.

In 1903, Mikulicz, referring to Bloch but not to Paul, strongly advocated the exteriorization operation for resection of malignant lesions of the colon. Like Bloch, Mikulicz simply exteriorized the segment of bowel containing the growth at the initial operative procedure and later cut it away (Fig. 5, *b*). That the name of Mikulicz, rather than Bloch or Paul, is associated with the exteriorization procedure in this country is largely due to the fact that Mikulicz described his method in a system of surgery published in this country in 1904.

Utilizing this fundamental principle, the two-stage exteriorization procedure was enlarged, reaching its ultimate development in the obstructive resection as described by Rankin[14] in 1930 (Fig. 5, *b*) and the modified Mikulicz resection as described by Lahey[7] in 1932 (Fig. 6). Both of these men demonstrated that this procedure could be made as radical in its scope as resection

with primary anastomosis and that it carried less risk of subsequent peritonitis which at that time was the commonest cause of death following resection of the colon. Lahey also demonstrated that this exteriorization procedure could be applied to lesions of the right colon, constructing a double barreled spur with the terminal ileum and transverse colon after resecting the right colon. After destruction of the spur this ileotransverse colostomy was closed by an extraperitoneal procedure, just as a double barreled colostomy on the left side. Today, as a result of more thorough preparation of the colon preoperatively, more adequate blood replacement during the operative procedure, refinements in technique, and the antibiotics, resection with primary anastomosis has gradually replaced the exteriorization procedure. This is graphically demonstrated by the figures from the Lahey Clinic where the modified Mikulicz resection

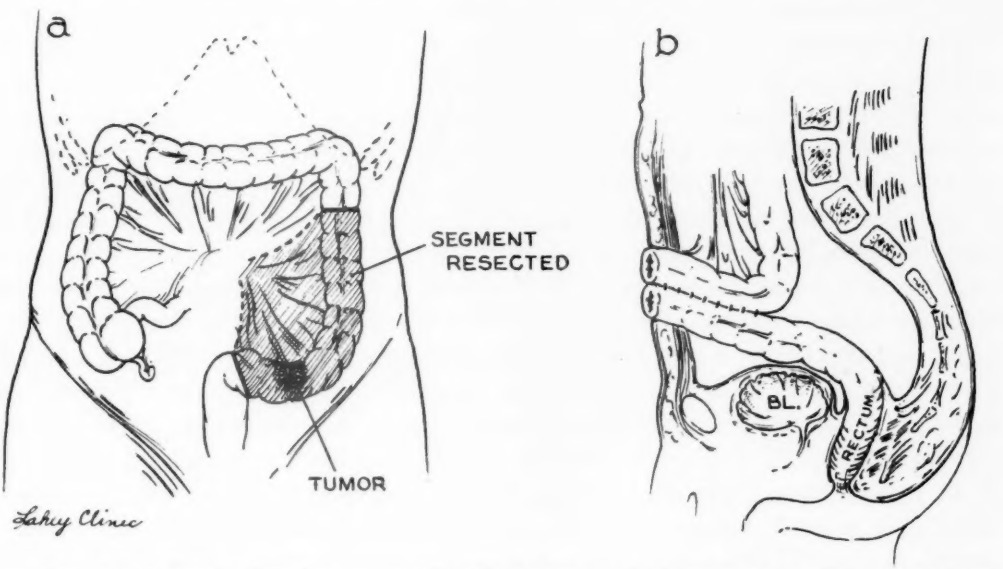

Fig. 6.—Modified Mikulicz resection (by Lahey). *a*, The wide extent of adjacent mesentery and bowel which are removed.
b, A long double barreled colostomy spur is constructed. The spur is obliterated by a crushing clamp and the colostomy closed by an extraperitoneal procedure.

received perhaps its widest employment (Table I). Marked degrees of obstruction associated with malignant disease of the left colon still call for preliminary cecostomy or transverse colostomy. Preliminary transverse colostomy is still indicated in colovesical fistulas secondary to diverticulitis. One is again struck not only by the logical reasoning of Paul but by the astuteness of his final conclusions.

COLOSTOMY IN MILITARY SURGERY

There remains a most interesting and important chapter in the story of colostomy, namely, its role in military surgery. This chapter is interesting because it has been written almost entirely in our own professional lifetime. It is of particular interest to those, who, as members of the Army or Navy Medical Corps during World War II, were privileged to have a small part in its writing.

TABLE I. OPERATIVE PROCEDURE, RESECTION FOR CARCINOMA OF COLON

YEAR	MODIFIED MIKULICZ		PRIMARY ANASTOMOSIS	
	CASES	PER CENT	CASES	PER CENT
1940	19	100	0	0
1945	36	80	9	20
1949	1	1.4	71	98.6

For many years, the operative treatment of perforating wounds of the abdomen was not advised under war conditions. Yet many military surgeons, disturbed by the high mortality rate associated with the conservative or expectant treatment of perforating wounds of the abdomen, thought that some of these patients could be saved by laparotomy with closure of the perforated bowel. Although a few of these battle casualties with perforating wounds of the abdomen were operated upon and recovered, British military surgeons, Bowlby and Wallace,[1] writing in 1917, thought that in the Spanish-American War and in the South African War the over-all results of surgical intervention had been unsatisfactory. Laparotomy had been associated with a mortality of 51 per cent during the South African War and they considered their own mortality of 50 per cent for the 1917 campaign of World War I to be encouraging from the standpoint of military surgery. (It should be noted that in both of these wars, laparotomy was attempted in only the most favorable cases.) They realized that the unsatisfactory results were due in most instances to the fact that these patients were operated upon too late. They also realized that intraperitoneal hemorrhage was a chief cause of death during the first few days following injury. They failed to realize the value of the exteriorization principle in treating perforating wounds of the colon since one of their axioms was that "artificial ani in the colon are to be avoided, if possible." They concluded that large intestinal wounds were mostly fatal, due largely to sepsis and that there was a high mortality associated with perforating wounds of the rectum.

It was during World War II that colostomy came into its own in the treatment of perforating wounds of the abdomen sustained in battle. Ogilvie,[12] the great British authority on military surgery of World War II, in reviewing the work of the British, Australian, and New Zealand surgeons in the Middle East during the early days of this war, stated that "the exteriorization of colon injuries is perhaps the greatest single factor in the improved results that they had been able to record." He also stated that they learned to apply the exteriorization principle to all injuries of the colon, even suspected ones, and to all parts of the large bowel. He also urged the construction of a double barreled spur whenever possible. He reported a mortality rate of 62.5 per cent for 350 cases of perforating wounds of the abdomen. This was compared with the 74 per cent associated with perforating wounds of the abdomen for World War I as given by Hamilton-Bailey[5] in *Surgery of Modern Warfare*. The figure of 62.5 per cent for World War II is particularly significant when we consider, as Ogilvie[12] pointed out, that in World War I laparotomy would never have been attempted in almost two-thirds of the patients who were operated upon during World War II. Moreover, his statistics for World War II included

a follow-up of these battle casualties at the Base Hospitals to which they were evacuated, which was not true in the figures given for World War I. As he pointed out, if this had not been done, 25 casualties who later died of their injuries would have been considered survivals. This late mortality following perforating wounds of the abdomen was appreciated by the surgeons of the United States Army Medical Corps[2, 3, 8] during the North African and early Italian campaigns. Some of these late deaths were the result of sepsis and frequently this sepsis was due to retraction of the exteriorized bowel below the surface of the abdominal wall. This resulted from inadequate mobilization of the colon at the time it was exteriorized.

Morgan,[11] an able British surgeon who was among the first to observe the application of modern preoperative and postoperative care to perforating wounds of the abdomen sustained in battle during the Middle East Campaign, concluded that "exteriorization of the damaged portion of the colon, when possible, is the safest procedure and closure of the perforation with complete exclusion by a proximal colostomy is the next best method of treating perforating wounds of the colon." He thought that any colostomy could be closed but that a long slack loop with limbs tacked together would make closure easier and safer. This was an opinion shared by many surgeons of the United States Army Medical Corps, particularly for extensive wounds of the colon and for wounds involving the mesenteric border. He reported a mortality for perforating wounds of the colon of 51.5 per cent, and a mortality of 40 per cent if these casualties were operated on in less than twelve hours. He also emphasized the markedly increased operability rate that was attained in World War II and pointed out that as more of these casualties were operated on, more lives could be saved, but that abdominal surgery on the battlefield would be associated with a prohibitive mortality unless it could be done with good anesthesia, good lighting, and adequate preoperative and postoperative care. He emphasized what had been noted by military surgeons in 1917, namely, that evacuation of abdominal casualties during the early postoperative period definitely increased the mortality rate. Debakey and Carter,[4] in reviewing the results of military surgery during World War II, found that the mortality from perforating wounds of the abdomen had been reduced from 45 per cent in World War I to 15 to 20 per cent during World War II. They believed that this reduced mortality was due to three main factors: first, the use of whole blood transfusions, second, the availability of trained, experienced surgeons close to the front line and third, the exteriorization of colon wounds and the use of colostomy for these and for perforating wounds of the rectum.

It may be that evacuation of the wounded by helicopter as has been done so extensively in Korea will permit battle casualties with perforating wounds of the abdomen to be operated upon under good operative conditions at a place where they can be held indefinitely and at the same time be operated upon even earlier than during World War II. Earlier operation, plus the more extensive use of the many antibiotics that are now available, will permit many wounds of the colon to be closed which were formerly exteriorized. Nevertheless, the

principle of exteriorization of a perforating wound of the colon or the establishment of a proximal colostomy when the injured segment cannot be exteriorized is now so firmly established in military surgery that it should only be departed from when operative conditions and subsequent experience indicate that it can be done with no increase in mortality.

CONCLUSIONS

The discovery of a nonsurgical cure for cancer and the total elimination of wars, both large and small, would mean the gradual disappearance of the operative procedure of colostomy. Until such time arrives, however, it will continue to occupy an important place in the surgery of the colon and rectum and will continue to be utilized either to save a patient's life or accepted as the price to be paid in return for the complete elimination of a life-destroying lesion such as cancer.

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Visceral Radiology. By Emerik Markovits, M. D. Pp. 594, with 681 illustrations. New York, 1951. The Macmillan Company. $24.00.

This book is a sequel to, and is patterned somewhat after, the author's book on *Bone and Joint Radiology.* Essentially the same style of writing and the same format are used in this book which makes it quite readable for either the radiologist or other members of the medical profession. The book contains 27 chapters under six major headings: The Respiratory System, The Circulatory System, The Digestive System, Abdomen and Abdominal Organs, Genito-Urinary System, and Central Nervous System. Each chapter of the book is introduced by a fundamental discussion of anatomy and physiology of the respective organs since the knowledge of the basic sciences is essential for conclusive interpretation of roentgenograms.

One part of the book will be discussed more thoroughly in order to show the general manner in which the entire book is written. The first major part, which is written on The Respiratory System, begins with a description of anatomy and physiology. The segments of the lungs are listed. This is followed by a brief but pertinent discussion of most of the major conditions involving the lungs with at least a brief mention of some of the rarer conditions. In discussing bronchostenosis, sketches of the effects of bronchostenosis upon the lobes and upon an entire lung are given. In discussing lobar pneumonia, sketches of the involvement of the different lobes are shown, as seen from the posteroanterior and lateral views. Under pulmonary cavitation there are found sketches of the formation of pulmonary cavities, such as might be seen on the roentgenogram of any given patient. Under bronchography, sketches of the different types of pathologic changes which may be recognized in a bronchogram are given. These sketches complement the actual reproduction of roentgenograms in the text since it would not be practical to reproduce roentgenograms depicting every stage and every type of change mentioned. Numerous tables of differential diagnosis of pulmonary conditions are given. Thirty-five conditions are listed as being capable of causing diffuse miliary densities in the lung fields and seventy-two causes of an enlarged hilar shadow are given.

This book is heartily recommended for the student trainee in radiology, the general practitioner, and the surgeon or internist who would like a concise reference text in diagnostic roentgenology.

Leibesubüngen mit Körperbeschädigten. Lorenzen, Ob. Stud. Rat H., Köln. Vol. 45. Pp. 218 with 182 illustrations. Stuttgart, 1951, Georg Thieme. Agents in U. S.: Grune & Stratton, New York. DM 7.50.

Normal recreation and sports activity can be enjoyed by many persons handicapped by amputations. This book outlines a program for group or individual rehabilitation with emphasis upon physical activity as recreation. Especially outstanding is the large amount of space devoted to swimming, diving, and life saving for amputees, with a complete discussion of the style most adapted to the various handicaps. A large number of excellent illustrations supplement the text. For those engaged in the rehabilitation of amputees, this book can be highly recommended.

Instrument and Apparatus in Orthopaedic Surgery. By E. J. Nangle, M.B., Ch.B., F.R.C.S., formerly Resident Surgical Officer, Royal National Orthopaedic Hospital, Stanmore and R.S.O. Wingfield-Morris Orthopaedic Hospital, Oxford Beit Fellow. Ed. 1, Pp. 231, with 200 illustrations. Springfield, Ill., 1951, Charles C Thomas, Publisher. $9.50.

Satisfactory results in the treatment of orthopedic patients depends largely upon a meticulous attention to apparently minor details in the choice, application, and adjustment of orthopedic appliances. Most common texts on orthopedic subjects mention these appliances only briefly. This book attempts to fill this hiatus and to acquaint the reader with the principles of action and the details of construction of a variety of splints and braces. It is not an exhaustive compendium of all such apparatus but rather a selection of those used by the author with success. Numerous illustrations are accompanied by an adequate description of the materials and methods of construction. An ample section is devoted to the use of plastics. A section on the use of respirators and the care of patients in respirators seems out of place in such a volume.

Fortschritte in der Behandlung Schwerer und Schwerster Hochspannungs-Unfaille. By Prof. Dr. H. Fischer, and Dr. R., Frohlicher, Zurich. Pp. 71 with 23 illustrations. 1951. DM 10.80. Agents in U. S.: Grune & Stratton, New York.

This report of the treatment of twelve patients with injuries received from contact with high-tension electric power lines deserves wide circulation among surgeons. In a thorough but concise manner, the principles of treatment are presented with an adequate documentation of the pertinent world literature. The problems are discussed in the order in which they present themselves: (1) the immediate myohemoglobinuria which frequently results in anuria, (2) shock, hemoconcentration, and hypoproteinemia resulting from fluid loss into the damaged tissue, and (3) the secondary tissue necrosis and infection. A comprehensive program of treatment based on clinical experience and laboratory investigation has been developed.

Immediate alkalinization of the urine by the administration of large amounts of sodium bicarbonate and sodium lactate is emphasized especially as a first aid measure since the maximum concentration of myohemoglobin in the urine is reached very rapidly. Diuresis is encouraged by giving large amounts of normal saline solution. Plasma should also be used. If anuria develops, one of the various methods of temporarily maintaining the status quo should be used. The authors prefer peritoneal lavage. Early amputation is recommended for severely damaged extremities before local fluid loss and toxic reabsorption further impairs the general condition of the patient. Antibiotics should be used prophylactically to combat infection.

That the results of this program of treatment are eminently satisfactory is evident from reading the protocols incorporated in the text. The authors have succeeded also in presenting their ideas and conclusions in a most interesting and well-integrated manner.

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